Official Title: MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

NCT Number: NCT04632992

Document Date: Protocol Amendment Version 6: 28-February-2023

TITLE:	**MYTACTIC: AN OPEN-LABEL PHASE II STUDY EVALUATING TARGETED THERAPIES IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH GENOMIC ALTERATIONS OR PROTEIN EXPRESSION PATTERNS PREDICTIVE OF RESPONSE**
PROTOCOL NUMBER:	ML42439
VERSION NUMBER:	6
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	152738
NCT NUMBER:	NCT04632992
TEST PRODUCT:	Entrectinib (RO7102122), Trastuzumab emtansine (RO5304020), Pertuzumab Trastuzumab Fixed Dose Combination Subcutaneous (PH FDC SC, RO7198574), Inavolisib (GDC-0077; RO7113755), Alectinib (RO5424802), Ipatasertib (RO5532961), Atezolizumab (RO5541267), Tucatinib, Pralsetinib (RO7499790), Tiragolumab (RO7092284)
SPONSOR:	Genentech, Inc.
***APPROVAL*:**	*See electronic signature and date 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	*20 January 2022*
4	19 July 2021
3	22 February 2021
2	10 November 2020
1	8 October 2020

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol ML42439 has been amended primarily to update safety information and to remove survival follow-up. Changes to the protocol and a rationale for each change are outlined below:

General Updates

- The study objective has shifted to look for short-term treatment response; therefore overall survival (OS) will no longer be analyzed and has been removed as a secondary endpoint (Sections 2.1.1, 5.3.5.8, and 6.4.2). Furthermore, it has been determined that the 1-year follow-up will not provide meaningful additional OS data considering the small sample size within each treatment group; therefore, follow-up visits/phone calls after the end of treatment (EOT) visit have been removed from the Schedule of Activities (SOA; SOA for each study arm). Additional language regarding survival follow-up has been updated to reflect these changes (Sections 3.1.1, 3.2, 4.6.1, 4.6.2; Section 4.6.3 was removed). Death will be reported as a safety endpoint.
- Due to the signal seeking nature of the study, tumor assessment images will no longer be submitted to an independent review facility. This language has been removed from the protocol (Sections 4.5.6 and 9.5).
- The disease control rate definition has been updated to “the proportion of patients whose best response is confirmed complete response (CR), confirmed partial response (PR), or a response of CR, PR, stable disease, or non-CR/non-progressive disease for a minimum of 98 days for 28-day cycle arms or 70 days for 21-day cycle arms after the first treatment date” to align with the statistical analysis plan (Sections 2.1.2 and 6.4.2).
- To align with previous updates, language regarding rescreening for a different treatment arm after disease progression has been removed (Section 3.1.1). This is no longer allowed.
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.8.6).
- Personal identifiable information (i.e., name) for the Medical Monitor has been removed from the protocol (title page). Sites are provided the Medical Monitor’s name separately and can contact the Medical Monitor via the Emergency Medical Call Center Help Desk (Section 5.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trials Regulation requirements (Section 8.4).
- Language was added to reflect that quality tolerance limits for monitoring patient safety and data integrity were established prior to study enrollment (Section 9.3).
- The URL for the Roche Global Policy on Sharing of Clinical Study Information has been updated (Section 9.6).

- Definitions of hepatotoxicity grades have been updated throughout to reflect the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5 (NCI CTCAE v5; Sections D.5.2.2.5, F.5.2.4.2, J.5.2.4.2, I.5.2.2.5, and I.5.2.3).
- It has been clarified that hematology/complete blood count (CBC) and chemistry tests for the EOT visit do not need to be repeated if done within 7 days prior to treatment discontinuation, unless clinically indicated (SOA for all study arms, except Arm C).
- It has been clarified that the blood sample at disease progression may be drawn within 7 days after disease progression (SOA for all study arms).
- Language has been clarified to indicate that the end of treatment visit must be done within 28 days after last study dose (SOA for all study arms).

Arm A: Entrectinib

- Note: because no patients were enrolled in this arm and the enrollment period is over, no updates were made to this treatment arm during this amendment (Appendix 10).

Arms D, K, L, M: Ipatasertib-specific Changes

- To account for ipatasertib's impact on glucose metabolism, instructions for taking ipatasertib have been updated to indicate it should be taken at least 2 hours after the last meal of the day, and patients should refrain from eating overnight (Sections D.4.2.2, K.4.2.2, L.4.2.2, and M.4.2.2).
- Management guidelines for dyslipidemia were added (Section D.5.2.2.9).
- Dermatologic toxicity guidelines for Arms K and L have been clarified (Sections K.5.2.2.3 and L.5.2.2.3).

Arms E, F, J, K, L, N: Atezolizumab-specific Changes

- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19, as well as Addendum 1 and Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (throughout sections and associated subsections of Sections E.5.2, F.5.2, J .5.2, K.5.2, L.5.2, and N.5.2). Adverse event management guidelines for overlapping toxicities were also updated accordingly (Sections F.5.2.4.1, J.5.2.4.1, K.5.2.2.3, and L.5.2.2.3).
- The list of identified risks for atezolizumab has been revised to include myelitis, facial paresis, and pericardial disorders. Additionally, hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab, and language has been revised accordingly (Sections E.5.1.1, F.5.1.2, J.5.1.2, K.5.1.2, L.5.1.2, and N.5.1.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Sections E.5.3, F.5.3, J.5.3, K.5.3, L.5.3, and N.5.3).
- Appendix 8 has 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.

- Appendix 8 has been revised to include autoimmune myelitis.

Arm N: Tiragolumab-specific Changes

- The required timing for thyroid function testing has been corrected and aligned to every 4 cycles (e.g. Cycles 1, 5, 9, 13, etc.) (Section N.6).
- To align with the Tiragolumab Investigator's Brochure, Version 7, the potential risks for tiragolumab have been updated to include lymphopenia and embryofetal toxicity (Section N.5.1.2). Additionally, immune-mediated hepatitis has been updated to an identified risk associated with tiragolumab (Section N.5.1.2).
- The dose modifications and treatment interruption sections have been moved to Section N.5.2.2 to align with combination treatment guidance for atezolizumab plus tiragolumab.
- Infusion-related reactions and cytokine-release syndrome management have been separated to align with the tiragolumab plus atezolizumab adverse event management guidelines (Sections N.5.2.2.7 and N.5.2.2.8).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**MYTACTIC: AN OPEN-LABEL PHASE II STUDY EVALUATING TARGETED THERAPIES IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH GENOMIC ALTERATIONS OR PROTEIN EXPRESSION PATTERNS PREDICTIVE OF RESPONSE**
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SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the CRO.

PROTOCOL SYNOPSIS

TITLE:	**MYTACTIC: AN OPEN-LABEL PHASE II STUDY EVALUATING TARGETED THERAPIES IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH GENOMIC ALTERATIONS OR PROTEIN EXPRESSION PATTERNS PREDICTIVE OF RESPONSE**
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PHASE:	Phase II
INDICATION:	Solid tumors
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of multiple therapies that are selected based on potential predictive biomarkers identified in patients with solid tumors.

EFFICACY

PRIMARY EFFICACY OBJECTIVE

The primary objective for this study is to evaluate the efficacy of various treatments and/or combinations of treatments in eligible patients with advanced unresectable or metastatic solid tumors, on the basis of the following endpoint:

- The primary endpoint for each arm of this study will be confirmed ORR (cORR) as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors. The cORR is defined as the proportion of patients whose confirmed best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease.

SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objectives for this study are to evaluate the efficacy of each targeted treatment on the basis of the following endpoints:

- Progression-Free Survival (PFS) defined as the time from start of treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- PFS rate at 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1.
- Disease control rate (DCR), defined as the proportion of patients *whose best response is confirmed CR, confirmed partial response (PR), or a response of CR, PR, stable disease (SD), or non-CR/non-progressive disease (PD) for a minimum of 98 days for 28-day cycle arms or 70 days for 21-day cycle arms after the first treatment date*.

EXPLORATORY EFFICACY OBJECTIVE

Exploratory efficacy objectives are to evaluate efficacy based following the following:

- Analysis of primary and secondary efficacy endpoints when subgrouped by basket, tumor site of origin, and/or self-reported race and ethnicity.

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of the study medications for the tumor types studied based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE [v5.0])
- Change from baseline in targeted clinical laboratory test results

BIOMARKERS OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are early surrogates of efficacy or relapse, are associated with a more severe disease state (i.e., prognostic biomarkers), are associated wit h acquired resistance to study drug(s), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- The association of baseline and changes in circulating tumor DNA (ctDNA) levels with response and progression to therapy.
- Determination of baseline and changes in expression or levels of biomarkers in the tumor tissue or blood that may be associated with response or resistance to therapy.

STUDY DESIGN

DESCRIPTION OF STUDY

OVERVIEW OF STUDY DESIGN

MyTACTIC is a Phase II, multicenter, non-randomized, open-label, multi-arm study designed to evaluate the safety and efficacy of targeted therapies as single agents or in rational, specified combinations in patients with advanced unresectable or metastatic solid tumors determined to harbor specific biomarkers. Patients will be enrolled based on local testing performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic laboratory. For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a

Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

The multi-arm structure of the MyTACTIC study allows patients with solid tumors to be treated with a drug or drug regimen tailored to their biomarker identified at screening. Each study treatment arm may have separate endpoints, screening, and treatment requirements, defined in the respective appendix. Futility analyses will be employed on all treatment arms to limit enrollment where evidence of very limited or lack of efficacy is observed.

During the study, the following biomarker samples will be collected:

Tumor tissue

- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

Blood samples

- Mandatory blood samples will be collected at screening, 8 weeks after first treatment, and at disease progression *(within 7 days after progression)* for analyses including ctDNA

These samples will be used to evaluate predictive and/or prognostic biomarkers, including but not limited to biomarkers related to driver oncogene signaling, response to study treatment, tumor pathogenesis, and mechanisms of resistance.

Treatment will be assigned by the treating investigator on the basis of relevant specified biomarkers, and will continue until radiographic disease progression (per RECIST v1.1; Response Assessment in Neuro-Oncology (RANO) Criteria for primary CNS tumors, or loss of clinical benefit for specific treatment arms, upon Medical Monitor *consultation*; unacceptable toxicity; patient or physician decision to discontinue; or death, whichever occurs first. If a patient discontinues treatment prior to disease progression (because of adverse event or other reason), tumor assessments will continue as specified in the treatment-specific appendix until disease progression, death, withdrawal of consent, or arm/study closure by the Sponsor, whichever occurs first.

Patients who do not meet the criteria for participation in this study (screen failure) or the timeline for the screening window may qualify for re-screening at the investigator's discretion. Patients must re-sign the consent form prior to rescreening. The investigator will record reasons for screen failure in the screening log.

NUMBER OF PATIENTS

Approximately 260 patients are anticipated to be enrolled at approximately 60 sites. Each arm will be limited to approximately 25 patients, with the exception of Arms M and O, which will be limited to approximately 10 patients.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following general inclusion criteria to be eligible to enroll in any treatment arm:

- Signed treatment-specific Informed Consent Form
- Positive biomarker results from a CLIA-certified or equivalently accredited diagnostic laboratory and availability of a full report of the testing results. This may be from a tissue or blood sample.
- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI: Sufficient archival tissue or a recent pretreatment tissue sample must be available for central testing (i.e. at least 11 slides or equivalent block) unless approved by Medical Monitor. If both archival and recent tissues are available, the recent tissue should be preferentially submitted.
- Age $\geq$ 18 years at time of signing Informed Consent Form

- Participation in a clinical trial is an appropriate treatment option, in the opinion of the investigator
- Ability to comply with the study protocol
- Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic solid malignancy
- Evaluable or measurable disease (i.e., at least one target or non-target lesion per RECIST V1.1 or one measurable or non-measurable lesion per RANO criteria for patients with primary CNS tumors)
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2
- Life expectancy ≥ 8 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC per arm-specific eligibility criteria
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 3 \times$ upper limit of normal (ULN), with the following exceptions:

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

    Patients with documented liver or bone involvement: ALP $\leq 5 \times$ ULN
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN
  - Serum creatinine $\leq$ 1.5 mg/dL or Glomerular filtration rate $>$ 50 mL/min/1.73 m2 as calculated through use of the Chronic Kidney Disease Epidemiology Collaboration equation

    Glomerular filtration rate (GFR) estimation: GFR=141 $\times$ min(Scr/κ, 1)α $\times$ max(Scr/κ, 1)-1.209 $\times$ 0.993Age $\times$ 1.018 [if female] $\times$ 1.159 [if black] where:
    Scr is serum creatinine in mg/dL,
    κ is 0.7 for females and 0.9 for males,
    α is -0.329 for females and -0.411 for males,
    min indicates the minimum of Scr/κ or 1, and
    max indicates the maximum of Scr/κ or 1
  - Albumin $\geq$ 25 g/L (2.5 g/dL)
- Agrees to take measures to prevent pregnancy in the patient or partner
- In addition to the general inclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific inclusion criteria for the respective arm as detailed in the treatment-specific appendix.

  Note: The requirements for enrollment into a specific arm may be more stringent.

Exclusion Criteria

Patients who meet any of the following criteria will be ineligible and excluded from study entry in any arm:

- Current participation or enrollment in another therapeutic clinical trial
- Eligible for an approved indication included in the local prescribing information for the applicable study treatment
- Symptomatic or actively progressing CNS metastases

  Asymptomatic patients with treated or untreated CNS metastases are eligible, provided that all of the following criteria are met:

  - No ongoing requirement for corticosteroids as therapy for CNS metastases, unless noted otherwise in the arm-specific appendix
  - No evidence of interim progression between the completion of CNS-directed therapy and screening radiographic study
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Evaluable disease must be present outside the CNS
- History of leptomeningeal disease, unless noted otherwise in the arm-specific appendix
- Wide field radiotherapy within 14 days prior to start of study treatment
- Stereotactic radiosurgery within 7 days prior to start of study treatment
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections, or any active infection that, in the opinion of the investigator, could impact patient safety
  - In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1; recovery of treatment-related toxicity consistent with other eligibility criteria
  - Androgen blockage may be continued for male patients with prostate cancer
- Patients known to be positive for HIV are excluded if they meet any of the following criteria:
  - CD4+ T-cell count of < 350 cells/μL
  - Detectable HIV viral load
  - History of an opportunistic infection within the past 12 months
  - On stable antiretroviral therapy for < 4 weeks
- Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exceptions:
  - Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
  - Patients with untreated HCV may be enrolled if the HCV is stable, the patient is not at risk for hepatic decompensation, and the intended treatment is not expected to exacerbate the HCV infection
  - Patients on concurrent HCV treatment may be enrolled if they have HCV below the limit of quantification
- Patients known to have active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test)
  - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA
- History of or concurrent serious medical condition or abnormality in clinical laboratory tests that, precludes the patient's safe participation in and completion of the study or confounds the ability to interpret data from the study (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
  - Patients with well-controlled comorbid disease on a stable treatment regimen for 4 weeks prior to screening are eligible for the study.

- History of malignancy other than disease under study within 3 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 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
- Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy of study treatment
- Major surgical procedure, other than for diagnosis, or significant traumatic injury within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or higher), myocardial infarction, or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmias, or unstable angina
- Pregnant or breastfeeding, or intending to become pregnant during the study
- In addition to the general exclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific exclusion criteria for the respective arm as detailed in the treatment-specific appendix.

  Note: The requirements for enrollment into a specific arm may be more stringent

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur approximately 1 year after the last patient is enrolled.

LENGTH OF STUDY

LPLV is expected to occur approximately 1 year after the last patient is enrolled.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Biomarker alteration	Study Treatment
ROS1 gene fusion	Arm A: Entrectinib
PIK3CA activating mutation	Arm B: Inavolisib (GDC-0077)
	Arm K: Ipatasertib + atezolizumab
ALK gene fusion	Arm C: Alectinib
AKT activating mutations and/or *PTEN* loss/loss of function	Arm D: Ipatasertib
	Arm L: Ipatasertib + atezolizumab
Co-mutation in PI3KCA activating mutation and AKT activating mutation or PI3KCA activating mutation and PTEN loss/loss of function	Arm M: Ipatasertib + paclitaxel
TMB ≥ 10/MSI-H/dMMR	Arm E: Atezolizumab + chemotherapy[a]
	Arm N: Atezolizumab + tiragolumab
ERBB2 gene mutation or amplification without known TMB ≥ 10/MSI-H/dMMR	Arm F: Trastuzumab emtansine + atezolizumab
	Arm G: PH FDC SC
	Arm H: PH FDC SC + chemotherapy [a]
	Arm I: Trastuzumab emtansine + tucatinib
ERBB2 gene amplification or mutation and TMB ≥10/MSI-H/dMMR	Arm J: Trastuzumab emtansine + atezolizumb
RET gene fusion	Arm O: Pralsetinib

chemo=chemotherapy; dMMR=deficient mismatch repair; HER2=human epidermal growth factor receptor 2; IV=intravenous; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; MSI-H=microsatellite instability high; PI3K=phosphatidylinositol 3-kinase; SC=subcutaneous; TMB=tumor mutational burden.

[a] Investigator's choice of docetaxel, paclitaxel, or capecitabine.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary endpoint for this study will be cORR as assessed by the investigator and according to the corresponding assessment criteria (RECIST v1.1 or RANO). The cORR is defined as the proportion of patients whose confirmed best response is a CR or PR for those

with measurable disease and CR for those with non-measurable disease. Confidence intervals at both 70% and 95% nominal levels will be reported using the Clopper-Pearson method. The primary efficacy endpoint will be computed for all treatment arms. If a patient receives at least one dose of study treatment and discontinues the study for any reason before confirmed response can be assessed, the patient will be considered a non-responder (not PR and not CR) and will be added to the denominator of the computation of cORR.

DETERMINATION OF SAMPLE SIZE

The focus for this study will be estimation since the study is composed of many single arms specific to a targeted therapy. Estimation of the primary endpoint will be 95% confidence intervals using the Clopper-Pearson method. As such, the maximum margin of error for sample sizes 25, 50, and 75 are 20.7%, 14.5%, and 11.8%, respectively. On a per arm basis, if the lower bound of the confidence interval is larger than a benchmark specific to that arm, then we will consider the given treatment as a significant improvement over the benchmark.

INTERIM ANALYSES

Non-binding Futility Analyses

For some arms, limited data are available regarding the efficacy and safety of the treatment across the eligible tumor population(s). Therefore, data from the first 12 efficacy-evaluable patients in a given arm will be used to conduct non-binding interim tumor agnostic futility analyses. Futility analyses for some arms may be conducted with the integration of data from other ongoing studies (see the Statistical Analysis Plan [SAP] for details). These analyses may be used to identify whether a treatment may be ineffective in a tumor agnostic population due to limited or lack of efficacy, and further accrual into such an arm may be stopped. Enrollment will not be stopped while awaiting results of the tumor agnostic futility analysis. To perform the analysis we will use Bayesian gating with arm-specific gating criteria and non-informative prior where futility will be declared if there is a posterior probability of greater than 60% that the true cORR is less than an arm-specific unacceptable level.

Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

ARM A: ENTRECTINIB IN PATIENTS WITH *ROS1* FUSION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm A: entrectinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm A: entrectinib treatment:

- *ROS1* gene fusion positivity, except patients with non-small cell lung cancer (NSCLC), as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' *ROS1* fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Ability to swallow entrectinib intact, without chewing, crushing, or opening the capsules/tablets

- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 5 weeks after the last dose of entrectinib; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of entrectinib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm A: entrectinib treatment:

- *ROS1* fusion-positive NSCLC
- Prior treatment with crizotinib
- Whole-brain radiotherapy and/or stereotactic radiosurgery for CNS disease within 14 days prior *to* the start of entrectinib treatment.
- Symptomatic or uncontrolled CNS involvement
  - Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.
  - Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment.
- Requirement for enzyme inducing anti-epileptic drugs (EIAEDs) or use within 14 days or 5 half lives (whichever is longer) prior to the start of entrectinib treatment
  - The use of seizure prophylaxis is allowed as long as patients are taking non-enzyme inducing anti-epileptic drugs (non-EIAEDs).
  - If patients require an anti-epileptic medication, a cytochrome (CYP) 3A4 non-EIAED can be used such as levetiracetam, valproic acid, gabapentin, topiramate, or lacosamide. Moderate inducers of CYP450, such as dexamethasone or other glucocorticoids, may be used at the discretion of the investigator.
- History of non-pharmacologically induced prolonged corrected QT (QTc) interval (e.g., repeated demonstration of a QTc interval $>$ 450 ms from ECGs performed at least 24 hours apart)
- History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction $\leq$ 50% observed during screening for the study
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome)
- Grade $\geq$ 2 peripheral neuropathy
- Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably affect drug absorption
- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor–induced pneumonitis

  Note: Radiation-induced lung disorders are not included in this exclusion criterion.

TEST PRODUCT (INVESTIGATIONAL DRUG)

Entrectinib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose of 600 mg/day (three 200-mg capsules per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. Modification may be needed in cases of coadministration with moderate or strong CYP3A4 inducers. For more specific dosing instructions, refer to the pharmacy manual.

ARM B: INAVOLISIB (GDC-0077) IN PATIENTS WITH *PIK3CA* ACTIVATING MUTATION-POSITIVE TUMORS

Target Population

To be enrolled in Arm B: inavolisib (GDC-0077) treatment, patients must have met and continue to meet all general eligibility criteria, in addition to arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm B: inavolisib (GDC-0077) treatment:

- *PIK3CA* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  - H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V
  - Other activating mutations with Medical Monitor approval
- ANC $\geq 1000/\mu L$ within 14 days prior to initiation of study treatment
- Fasting glucose < 126 mg/dL and glycosylated hemoglobin (HbA_{1c}) $< 5.7\%$
- Willingness and ability to swallow GDC-0077 intact, without chewing, or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 60 days after the last dose of inavolisib (GDC-0077); and agreement to refrain from donating eggs during this same period. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 120 days after the last dose of inavolisib (GDC-0077), and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm B: inavolisib (GDC-0077) treatment:

- Primary CNS tumors
- Type 2 diabetes requiring antihyperglycemic medication or any history of type 1 diabetes

  Patients with elevated fasting glucose at baseline (fasting glucose $\geq$ 126 mg/dL [$\geq$ 7.0 mmol/L]) or HbA1c $\geq$ 5.7% will be excluded from the study
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Uncontrolled pleural effusion or ascites requiring recurrent drainage procedures twice monthly or more frequently

  Indwelling pleural or abdominal catheters are allowed provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved

- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator and/or study ophthalmologist, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Patients requiring any daily supplemental oxygen
- History of or active inflammatory disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)

  Patients currently receiving immunosuppressants (e.g., sulfasalazines) are considered to have active disease and are, therefore, ineligible.
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
- Clinically significant and active history of liver disease, including severe liver impairment (ChildPugh score B/C), current alcohol abuse, or cirrhosis
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $>$ 470 ms demonstrated by at least two ECGs $>$ 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval
- Allergy or hypersensitivity to components of the inavolisib (GDC-0077) formulation
- Any symptomatic active lung disease, including pneumonitis

TEST PRODUCT (INVESTIGATIONAL DRUG)

Inavolisib (GDC-0077) will be self-administered by patients orally at home (except on clinic days) at the same time each day, on a starting dose of 9 mg/day (one 9-mg tablet per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM C: ALECTINIB IN PATIENTS WITH *ALK* REARRANGEMENT-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm C: alectinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm C: alectinib treatment:

- *ALK* gene fusion positivity, in indications other than non-small cell lung cancer (NSCLC), as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' *ALK* fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment

- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib; and agreement to refrain from donating eggs during this same period.
- For males with female partners of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm C: alectinib treatment:

- ALK-positive NSCLC
- Inability to swallow pills
- Any gastrointestinal disorder that may affect absorption of oral medications, such as refractory vomiting, malabsorption syndrome, external biliary shunt, or significant bowel resection that would preclude absorption of alectinib
- Detection of the following *ALK* point mutations: I1171N/S, G1202R
- Symptomatic or uncontrolled CNS involvement
  - Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.
  - Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of alectinib treatment.
- Liver disease, characterized by any of the following:
  - Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices
  - Active autoimmune, alcoholic, or other types of acute hepatitis
- History of organ transplant
- Symptomatic bradycardia
- History of hypersensitivity to any of the additives in the alectinib drug formulation

  This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.

TEST PRODUCT (INVESTIGATIONAL DRUG)

Alectinib will be self-administered by patients orally at home (except on clinic days), at the same times each day, on a starting dose of 600 mg (four 150-mg capsules) twice a day (BID) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM D: IPATASERTIB IN PATIENTS WITH PTEN LOSS-OF-FUNCTION OR *AKT1/2/3* MUTANT-POSITIVE SOLID TUMORS

TARGET POPULATION

To be enrolled in Arm D: ipatisertib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm D: ipatasertib treatment:

- *AKT1/2/3* mutant positivity or PTEN loss of function, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  – *AKT1*: E17K; L52R; Q79K

  – *AKT2*: E17K

  – *AKT3*: E17K; L51R; Q78K

  PTEN loss of function is defined as PTEN dominant negative missense mutations or deleterious in-frame and missense mutations affecting protein function

  Other applicable mutations are eligible with Medical Monitor approval

  or PTEN protein loss as determined by a CLIA or equivalently certified immunohistochemistry assay
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib without chewing *or crushing the tablets*
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm D: ipatasertib treatment:

- Triple negative adenocarcinoma of the breast (TNBC)

  TNBC tumors are defined as HER2 negative, estrogen receptor (ER) negative, and progesterone receptor (PgR) negative:

  – ER or PgR negativity is defined as $<$1% of tumor cell nuclei immunoreactive to the respective hormonal receptor

  – HER2 negativity is assessed by IHC and/or in situ hybridization according to 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of >10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Uncontrolled pleural effusion, pericardial effusion, or ascites

TEST PRODUCT (INVESTIGATIONAL DRUG)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM E: ATEZOLIZUMAB PLUS CHEMOTHERAPY IN PATIENTS WITH TMB-H/ MSI-H/DMMR-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm E: atezolizumab plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm E: atezolizumab plus chemotherapy treatment:

- Documentation of one of the following biomarkers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified assay (tissue or blood):
  - Tumor mutational burden-high (TMB-H), defined as ≥ 10 mutations per megabase*, as determined by a tissue-based NGS assay*
  - Microsatellite instability high (MSI-H)
  - Deficient mismatch repair (dMMR)
- ANC $\geq 1500/\mu L$ within 14 days prior to initiation of study treatment
- Lymphocyte count $\geq 500/\mu L$
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period.

- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 3 months after the last dose of chemotherapy and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm E: atezolizumab plus chemotherapy treatment:

- Primary CNS tumors with any of the following characteristics:
  - History of intracranial hemorrhage or spinal cord hemorrhage
  - Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1
- Metastases to the midbrain, pons, medulla, or spinal cord
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium $>$ upper linit of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of 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
  - 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 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
    - 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.
- Active tuberculosis
- Treatment with therapeutic oral or intraveneous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti-cytotoxic T–lymphocyte-associated protein 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

  – Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment

  – No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events version 5.0 [NCI CTCAE v5.0] Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit *in consultation with the* Medical Monitor).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

ARM F: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm F: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizuamb, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 *as determined by a tissue-based NGS assay*, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin > 500 mg/m^2

  - Liposomal doxorubicin $>$ 500 mg/m^2
  - Epirubicin $>$ 720 mg/m^2
  - Mitoxantrone $>$ 120 mg/m^2
  - Idarubicin $>$ 90 mg/m^2

    If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic $>$ 150 mmHg and/or diastolic $>$ 100 mmHg)
  - Inadequate left ventricular ejection fraction at baseline, $<$ 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - History of symptomatic congestive heart failure Grade $\geq$ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  - History of decrease in left ventricular ejection function to $<$ 40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade $\geq$ 2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ upper limite of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade $\geq$ 3 peripheral neuropathy, as defined by National Cancer Institute Common Terminology Criteria for Research Adverse Events version 5.0 [NCI CTCAE v5.0]
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of 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
  - 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 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
- 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

- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain

  Patients requiring 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 $\geq$ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade $\leq$ 1) prior to study treatment initiation

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha (TNF-α) agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab will be administered first followed by trastuzumab emtansine. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor *consultation*). Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes > 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

ARM G: PH FDC SC IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm G: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm G: PH FDC SC treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥ 1000/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (within 3 months) left ventricular ejection fraction (LVEF) ≥ 50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)

- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm G: PH FDC SC treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 *as determined by a tissue-based NGS assay*, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- In addition to the core exclusion criterion for significant cardiovascular disease, patients will be excluded if they have any of the following:
  - High-risk arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

TEST PRODUCT (INVESTIGATIONAL DRUG)

PH FDC SC is given as a fixed dose (i.e. non-weight based) by SC injection. Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since a prior dose of

Perjeta and Herceptin intravenous (IV) or PH FDC subcutaneous (SC) at study entry, or have had ≥6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

ARM H: PH FDC SC PLUS CHEMOTHERAPY IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm H: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm H: PH FDC SC plus chemotherapy treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥ 1500/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (witin 3 months) left ventricular ejection fraction (LVEF) ≥50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or for 3 months after the last dose of chemotherapy, whichever is longer, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm H: PH FDC SC plus chemotherapy treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 *as determined by a tissue-based NGS assay*, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- In addition to the core exclusion criterion for significant cardiovascular disease, patients will be excluded if they have any of the following:
  - High-risk arrhythmias (i.e., atrial tachycardia with a heart rate $\geq$100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC
- Current chronic daily treatment with corticosteroids (dose $>$ 10 mg methylprednisolone or equivalent excluding inhaled steroids)

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

PH FDC SC is given as a fixed dose (i.e. non-weight based) by SC injection. Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since a prior dose of Perjeta and Herceptin intravenous (IV) or PH FDC SC at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

ARM I: TRASTUZUMAB EMTANSINE PLUS TUCATINIB IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm I: trastuzumab emtansine plus tucatinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  – Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  – Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  – Transmembrane domain: S653C; V659E; G660D; R678Q

  – GFR domain IV: P551L; R552S

  – Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last administration of tucatinib, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last dose of tucatinib, whichever is longer and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 *as determined by a tissue-based NGS assay*, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  – Doxorubicin > 500 mg/m^2
  – Liposomal doxorubicin > 500 mg/m^2

  - Epirubicin > 720 mg/m^2
  - Mitoxantrone > 120 mg/m^2
  - Idarubicin > 90 mg/m^2

    If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine or tucatinib formulations
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - Inadequate left ventricular ejection fraction at baseline, $< 50\%$ by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  - History of decrease in left ventricular ejection function to $< 40\%$ or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade ≥ 2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis
- Have used a strong cytochrome P450 (CYP)2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 day prior to start of treatment
- Grade ≥ 3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia

TEST PRODUCT (INVESTIGATIONAL DRUG)

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes $> 10\%$ compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

Tucatinib drug product may be supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

ARM J: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH *ERBB2*-AMLIFICATION OR MUTATAION AND TMB-H/MSI-H/DMMR TUMORS

TARGET POPULATION

To be enrolled in Arm J: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  – Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  – Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  – Transmembrane domain: S653C; V659E; G660D; R678Q

  – GFR domain IV: P551L; R552S

  – Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Documentation of one of the following biomarkers, as determined by a CLIA or equivalently certified assay (tissue or blood):
  – Tumor mutational burden high (TMB-H) high, defined as ≥ 10 mutations per megabase*, as determined by a tissue-based NGS assay*
  – Microsatellite instability high (MSI-H)
  – Deficient mismatch repair (dMMR)
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizuamb, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer
- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin > 500 mg/m^2
  - Liposomal doxorubicin > 500 mg/m^2
  - Epirubicin > 720 mg/m^2
  - Mitoxantrone > 120 mg/m^2
  - Idarubicin > 90 mg/m^2

    If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg)
  - Inadequate left ventricular ejection fraction (LVEF) at baseline, $<50\%$ by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) or Class $\geq$ II New York Heart Association
  - History of decrease in left ventricular ejection function to $< 40\%$ or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade ≥ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium $>$ upper limite of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade ≥ 3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of 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

- 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 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
    - 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
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain

  Patients requiring 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 ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (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–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

TEST PRODUCT (INVESTIGATIONAL DRUG)

Atezolizumab will be administered first followed by trastuzumab emtansine. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor *consultation*). Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes $>$ 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

ARM K: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PIK3CA ACTIVATING MUTATION POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm K: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm K: ipatasertib in combination with atezolizumab treatment:

- PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  – H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V

  – Kinase domain: T733I; L755P/S; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); L755P/S/_T759del; G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  Other activating mutations with Medical Monitor approval
- No available acceptable treatment for malignancy that is expected to provide clinical benefit
- ANC $\geq$ 1000/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A1c (HbA1c) $\leq$7.5%
- Ability to swallow ipatasertib intact, without chewing or crushing the tablets

- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm K: ipatasertib plus atezolizumab treatment:

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

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 enrollment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  – 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.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor
  - Up to approximately 12 such patients may be enrolled
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Prior treatment with ipatasertib or other Akt inhibitors
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$ 2 weeks prior to initiation of study treatment are eligible for enrollment.

  Diabetic patients with fasting total serum glucose $>$ 8.3 mmol/L (150 mg/dL) and/or HbA1C $>$ 7.5 are not eligible for enrollment.
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)

- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Uncontrolled pleural effusion, pericardial effusion, or ascites

TEST PRODUCT (INVESTIGATIONAL DRUG)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit upon Medical Monitor *consultation*).

ARM L: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PTEN LOSS/ LOSS OF FUNCTION OR AKT ACTIVATING MUTATION–POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm L: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm L: ipatasertib in combination with atezolizumab treatment:

- AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  – AKT1: E17K; L52R; Q79K
  – AKT2: E17K
  – AKT3: E17K; L51R; Q78K

  or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay
- No available acceptable treatment for malignancy that is expected to provide clinical benefit
- ANC $\geq$ 1000/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A1c (HbA1c) $\leq$7.5%
- Ability to swallow ipatasertib intact, without chewing *or crushing the tablets*
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period.

- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm L: ipatasertib plus atezolizumab treatment:

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

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 enrollment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  – 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.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor
  - Up to approximately 12 such patients may be enrolled
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Prior treatment with ipatasertib or other Akt inhibitors
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$ 2 weeks prior to initiation of study treatment are eligible for enrollment.

  Diabetic patients with fasting total serum glucose $>$ 8.3 mmol/L (150 mg/dL) and/or HbA1C $>$ 7.5 are not eligible for enrollment.
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)

- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Uncontrolled pleural effusion, pericardial effusion, or ascites

TEST PRODUCT (INVESTIGATIONAL DRUG)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor *consultation*).

ARM M: IPATASERTIB PLUS PACLITAXEL IN PATIENTS WITH CO-MUTATIONS IN PIK3CA ACTIVATING MUTATIONS AND PTEN LOSS/ LOSS-OF-FUNCTION OR AKT ACTIVATING MUTATION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm M: ipatasertib in combination with paclitaxel treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm M: ipatasertib in combination with paclitaxel treatment:

- A co-mutation of either PIK3CA activating mutation and AKT activating mutation or a PIK3CA activating mutation and PTEN loss or loss of function based on the following biomarkers:
  - PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

    PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:
    - H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V
    - Other activating mutations with Medical Monitor approval
  - AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

    AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:
    - AKT1: E17K; L52R; Q79K
    - AKT2: E17K
    - AKT3: E17K; L51R; Q78K

    or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay
- ANC $\geq$ 1500/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A1c (HbA1c) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing *or crushing the tablets*

- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 6 months after the last dose of paclitaxel, whichever occurs later, and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and 3 months after the last dose of paclitaxel, whichever occurs later and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm M: ipatasertib in combination with paclitaxel treatment:

- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) <50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of >10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Uncontrolled pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain
  - Patients requiring 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 ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation
  - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium, > 12 mg/dL calcium, or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia

- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Prior treatment with an Akt inhibitor
- Note that prior PI3K or mTOR inhibitors are allowed.
- Known hypersensitivity or contraindication to any component of the study treatments, including the paclitaxel excipient macrogolglycerol ricinoleate
- Grade $\geq$ 2 peripheral neuropathy
- Prior treatment with paclitaxel treatment

TEST PRODUCT (INVESTIGATIONAL DRUG)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) *on days 1 through 21 of 28-day cycles* until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib.

ARM N: ATEZOLIZUMAB PLUS TIRAGOLUMAB IN PATIENTS WITH TMB-H/MSI-H/DMMR-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm N: atezolizumab plus tiragolumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm N: atezolizumab plus tiragolumab treatment:

- Documentation of one of the following biomarkers, as determined by a CLIA or equivalently certified assay (tissue or blood):
  - Tumor mutational burden high (TMB-H) high, defined as $\geq$ 10 mutations per megabase*, as determined by a tissue-based NGS assay*
  - Microsatellite instability high (MSI-H)
  - Deficient mismatch repair (dMMR)
- ANC $\geq$ 1200/μL within 14 days prior to initiation of study treatment
- Lymphocyte count $\geq$500/μL
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2
- For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 90 days after the final dose of tiragolumab or 5 months after the last dose of atezolizumab, whichever is later; and agreement to refrain from donating eggs during this same period.

- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 90 days after the last dose of tiragolumab and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm N: atezolizumab plus tiragolumab treatment:

- Primary CNS tumors with any of the following characteristics:
  - History of intracranial hemorrhage or spinal cord hemorrhage
  - Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1
- Metastases to the midbrain, pons, medulla, or spinal cord
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ upper limit of normal [ULN])
- Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exception (note that this is more stringent than the core criterion):

  Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- Positive EBV viral capsid antigen IgM test at screening

  An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  - 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.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-TIGIT, anti-LAG3, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti-CTLA-4 treatment may be enrolled, provided the following requirements are met:
  - Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment
  - No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events [NCI CTCAE] Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 after Medical Monitor *consultation*
  - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
  - Any prior Grade ≥ 3 immune-mediated adverse event or any unresolved Grade > 1 immune-mediated adverse event while receiving any previous immunotherapy agent other than immune checkpoint blockade agents
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation

TEST PRODUCT (INVESTIGATIONAL DRUG)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor *consultation*). Atezolizumab should be administered prior to tiragolumab on days when both are administered.

Following the administration of atezolizumab and an observation period, patients will receive 600 mg tiragolumab at a fixed dose administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab dose is fixed and is not dependent on body weight.

ARM O: PRALSETINIB IN PATIENTS WITH RET FUSION-POSITIVE TUMORS

TARGET POPULATION

To be enrolled in Arm O: pralsetinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

ADDITIONAL INCLUSION CRITERIA

Patients must meet the following additional inclusion criteria for entry into Arm O: pralsetinib treatment:

- RET fusion positivity, except patients with non-small cell lung cancer (NSCLC) or thyroid cancers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' RET fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Ability to swallow pralsetinib intact, without chewing, crushing, or opening the capsules/tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 14 days after the last dose of pralsetinib; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 7 days after the last dose of pralsetinib, and agreement to refrain from donating sperm during this same period.

ADDITIONAL EXCLUSION CRITERIA

Patients who meet any of the following additional criteria will be excluded from entry into Arm O: pralsetinib treatment:

- RET fusion-positive NSCLC
- RET fusion-positive thyroid cancer
- Patient's tumor has any additional known primary driver alterations other than RET, such as targetable mutations of EGFR, ALK, ROS1, MET, KRAS or BRAF.
- Known history of hypersensitivity to pralsetinib or any of its excipients
- Prior treatment with RET inhibitors (approved or investigational)
- Note: Other prior anti-cancer therapy is allowed
- Screening QT interval corrected using Fridericia's formula (QTcF) $>$480 milliseconds, history of prolonged QT syndrome or torsades de pointes, and/or familial history of prolonged QT syndrome
- History of pneumonitis during the prior 12 months
- Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids $>$10 mg/day of prednisone (or equivalent)

- Active, uncontrolled infection (viral, bacterial, or fungal)
  - Participants with controlled infections who are stable on treatment may be eligible if the benefit–risk assessment is justified
- Clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
- Neutrophil growth factor support within 14 days of the first dose of study drug
- Treatment with a prohibited medication or herbal remedy that cannot be discontinued at least 14 days before the start of study drug administration.

TEST PRODUCT (INVESTIGATIONAL DRUG)

Pralsetinib will be self-administered by patients orally at home, at the same time each day, on a starting dose of 400 mg/day (four 100 mg capsules per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab	antibody
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
AML	acute myeloid leukemia
ARDS	Acute respiratory distress syndrome
ARR	Administration-related reaction
ASCO	American Society of Clinical Oncology
ASTCT	American Society for Transplantation and Cellular Therapy
AV	atrioventricular
BAL	bronchoalveolar lavage
BID	twice a day
BiPAP	bi-level positive airway pressure
CAR	chimeric antigen receptor
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
cORR	confirmed ORR
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CR	complete response
CRF	Case Report Form
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Abbreviation	Definition
CTLA-4	cytotoxic T–lymphocyte-associated protein 4
CYP	cytochrome
DCR	Disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DOR	duration of objective response
DPP4	dipeptidyl peptidase 4
DTC	differentiated thyroid cancer
EBV	epstein-barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECMO	extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EIAED	enzyme inducing anti-epileptic drugs
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ER+	estrogen receptor positive
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FLAIR	fluid-attenuated inversion recovery
FISH	fluorescence in situ hybridization
FMI	Foundation Medicine, Inc.
FNA	Fine needle aspiration
FSP	Functional Service Provider
G-CSF	granulocyte colony-stimulating factor
GDFN	glial cell line-derived neurotrophic factors
GM-CSF	granulocyte-macrophage colony-stimulating factor
GFR	Glomerular filtration rate
GFRα	GDNF family receptors-α
GI	gastrointestinal
HbA_{1c}	hemoglobin A1c
HBcAb	hepatitis B core antibody

Abbreviation	Definition
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2 negative
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HR+	hormone receptor positive
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICU	intensive care unit
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IMT	inflammatory myofibroblastic tumors
IND	Investigational New Drug (application)
IR	incomplete response
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IxRS	Interactive Voice Response System
LDAC	low-dose cytarabine
LFT	liver function test
LOF	loss-of-function
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAb	monoclonal antibody
MASC	mammary analogue secretory carcinoma
MAP	mitogen-activated protein
MAS	macrophage activation syndrome
MKI	multikinase inhibitors
MRI	magnetic resonance imaging

Abbreviation	Definition
MSI-H	microsatellite instability high
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multiple-gated acquisition
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer
NRH	nodular regenerative hyperplasia
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PE	polyethylene
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function tests
P-gp	P-glycoprotein
PH FDC SC	fixed dose combination of pertuzumab and trastuzumab administered subcutaneously
PI3K	phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIP2	phosphatidylinositol-4,5-bisphosphate
PIP3	phosphatidylinositol-3,4,5-triphosphate
PK	pharmacokinetic
PO	by mouth
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PTEN	phosphatase and tensin homolog
QD	once a day
QTc	corrected Q-T interval
QTcF	QT interval corrected using Fridericia's formula

Abbreviation	Definition
RAI	radioactive iodine
RANO	Response Assessment in Neuro-Oncology
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RET	Rearranged during Transfection
S6RP	S6 ribosomal protein
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	stable disease
SGLT2	sodium-glucose transport protein 2
SLL	small lymphocytic lymphoma
SLS	sodium lauryl sulfate
SMCC	succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate
STAT	statim (immediately)
T3	triiodothyronine
T4	thyroxine
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TLS	tumor lysis syndrome
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
TNBC	triple negative adenocarcinoma of the breast
TNF-α	tumor necrosis factor-alpha
TPS	tumor proportion score
TSH	thyroid stimulating hormone
ULN	upper limit of normal
U.S.	United States
VAD	ventricular assist device
WES	whole exome sequencing
WGS	whole genome sequencing
WT	wild type

1. BACKGROUND

Oncology is rapidly evolving into a more personalized healthcare approach. Improved understanding of the role of cancer biomarkers, further development of molecular-targeted therapies, and the standardization of appropriate targeted treatment into treatment guidelines have shifted clinical practice to utilize genomic information as an integral component of clinical decision-making (Kris et al. 2014; Barlesi et al. 2016). Therapies that specifically target actionable oncogenic drivers have become the cornerstone of precision oncology.

Currently, targeted agents are approved for use in specific cancer types (as defined by primary site), or a subset of that population harboring the specific molecular alteration. Usually, targeted agents have been approved in the cancer types that most frequently carry the specific molecular target. However, it is now clear that molecular alterations can be found in cancers from other primary sites, although often at low incidence levels. The potential therapeutic importance of these abnormalities is not clear, although anecdotal reports have documented activity with the investigational use of appropriate targeted therapy (Cappuzzo et al. 2006; Masago et al. 2009; LoRusso et al. 2011; Masago et al. 2011; Kelly et al. 2012; Minor et al. 2012). With the relative rarity of these alterations (usually $<5\%$) in any specific cancer type, it is difficult to identify sufficient patients for clinical trials.

With these recent advancements, numerous platforms have been developed to survey the cancer cell genome and detect critical molecular alterations. With increased molecular profiling, gene alterations for which a targeted agent exists, or are associated with improved efficacy of cancer immunotherapies, are being identified more frequently in tumor types for which these agents are currently not approved. These findings present a new opportunity to test the efficacy of available targeted agents and immunotherapies.

In addition, there have been recent drug approvals in pan-tumor indications paving the way for registration for molecular alterations in multiple tumor types.

For example, entrectinib (Rozlytrek™) was approved in the United States based on the results in 51 adult patients across three clinical trials. A pooled analysis of 3 Phase I-II studies investigating patients with locally-advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer demonstrated that treatment with entrectinib induced a durable and clinically meaningful response. Among the efficacy-evaluable patients, 77% had an objective response, with a median duration of response of 24.6 months (95% CI 11.4-34.8) (Drilon et al. 2020). The same analysis investigated patients with metastatic or locally advanced solid tumors harboring a fusion in the NTRK gene (NTRK1, NTRK2, or NTRK3), comprising of 10 different tumor types and 19 different histologies. Similarly, treatment with entrectinib demonstrated a durable and clinically meaningful response, showing Entrectinib to be a viable treatment option for patients with NTRK

fusion-positive solid tumors. An objective response was observed in 57% of the evaluable patients (95%CI 43.2-70.8), with 4 complete responses and 27 partial responses. The median duration of response was 10 months (95% CI 7.1 to NE), (Doebele et al. 2019).

Tumor mutational burden has been associated with treatment outcomes with cytotoxic T−lymphocyte-associated protein 4 (CTLA-4) and programmed death-ligand 1 (PD-L1) inhibitors. Pembrolizumab (Keytruda®) was granted accelerated approval by the FDA for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors, defined as ≥10 mutations/megabase (mut/Mb). The Phase II basket study of pembrolizumab monotherapy in this patient population demonstrated that TMB-H was associated with higher response rates in a number of different unresectable or metastatic tumor types, suggesting that tumor mutational burden (TMB) may predict efficacy of pembrolizumab treatment.

In addition to testing targeted therapies in a pan-tumor setting, this study aims to expand study access to patients that are traditionally underrepresented in clinical trials. Classical registrational clinical trials often underrepresent patients of color, with data indicating that 88% of genetic sequencing/association studies have been done in individuals of European decent. In addition, industry study design standards may unintentionally prevent diverse patients from being enrolled, as most studies include certain inclusion/exclusion criteria that tend to exclude people of specific ethnicities. This study will focus on inclusion of underrepresented, understudied patients with broader entry criteria and with an emphasis on recruiting patients of color to ensure this study reflects the US population more accurately.

Specific biomarkers of interest for this protocol and their respective targeted therapies are outlined in Table 1. Background and rationale for the biomarkers and the associated targeted therapies, are provided in the sections below.

Table 1 Biomarker-specific Study Treatments

Biomarker alteration	Study Treatment	Appendix
ROS1 gene fusion	Arm A: Entrectinib	Appendix 10
PIK3CA activating mutation	Arm B: Inavolisib (GDC-0077)	Appendix 11
	Arm K: Ipatasertib + atezolizumab	Appendix 20
ALK gene fusion	Arm C: Alectinib	Appendix 12
AKT activating mutations and/or PTEN loss/loss of function	Arm D: Ipatasertib	Appendix 13
	Arm L: Ipatasertib + atezolizumab	Appendix 21
Co-mutation in PI3KCA activating mutation and AKT activating mutation or PI3KCA activating mutation and PTEN loss/loss of function	Arm M: Ipatasertib + paclitaxel	Appendix 22
TMB ≥ 10/MSI-H/dMMR	Arm E: Atezolizumab + chemotherapy[a]	Appendix 14
	Arm N: Atezolizumab + tiragolumab	Appendix 23
ERBB2 gene mutation or amplification without known TMB ≥ 10/MSI-H/dMMR	Arm F: Trastuzumab emtansine + atezolizumab	Appendix 15
	Arm G: PH FDC SC	Appendix 16
	Arm H: PH FDC SC + chemotherapy [a]	Appendix 17
	Arm I: Trastuzumab emtansine + tucatinib	Appendix 18

Biomarker alteration	Study Treatment	Appendix
ERBB2 gene amplification or mutation and TMB ≥10/MSI-H/dMMR	Arm J: Trastuzumab emtansine + atezolizumb	Appendix 19
RET gene fusion	Arm O: Pralsetinib	Appendix 24

dMMR=deficient mismatch repair; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; MSI-H=microsatellite instability high; PI3K=phosphatidylinositol 3-kinase; RET=Rearranged during Transfection; TMB=tumor mutational burden.

[a] Investigator's choice of docetaxel, paclitaxel, or capecitabine.

1.1 BACKGROUND AND RATIONALE FOR MOLECULARLY-TARGETED THERAPIES

Cancer treatment is evolving toward a more personalized approach where the intersection of genomics, pathology, and classical imaging methods lead to individualized cancer care. As novel genomic alterations and other biomarkers are identified, research evolves and leads to customized targeted treatments. A clinical trial matching therapy choice to tumor biomarkers has the potential to yield valuable clinical information and provide meaningful treatment options for patients.

1.1.1 Arm A: Entrectinib Treatment for Tumors with ROS1 Gene Fusions

ROS1 belongs to the insulin-receptor superfamily. Upon activation, it plays a role in relaying cell signals from the extracellular environment to the nucleus thereby promoting cell proliferation and cell survival. ROS1 gene rearrangements create fusion proteins with constitutively active kinase domains that then activate downstream cell signaling pathways. These pathways include Ras/ERK for cellular proliferation and the JAK-STAT and phosphoinositide 3-kinase (PI3K)/AKT pathways, which regulate cell survival (anti-apoptosis) and proliferation. ROS1 fusion proteins may also activate the mammalian target of rapamycin (mTOR) pathway, which is critical for the regulation of protein translation. Cancers that have these pathways activated tend to be more aggressive, with invasion and metastasis leading to poor survival for patients (Davies and Doebele 2013).

ROS1 fusion partners have been identified in patients with non-small cell lung cancer (NSCLC), and ROS1 gene rearrangements have also been detected in other tumor types including glioblastoma multiforme, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma (Davies et al. 2012; Davies and Doebele 2013; Lee et al. 2013; Shaw et al. 2013). The prevalence of ROS1 gene fusions across solid tumors excluding NSCLC is ~0.05% (Hartmaier et al. 2017; Foundation Medicine 2019).

Several small-molecule inhibitors have been developed to treat tumors harboring ROS1 oncogenic fusion kinases (e.g., the ROS1 inhibitors crizotinib and entrectinib, which have demonstrated targeted activity against lung cancers harboring ROS1 gene rearrangements).

Crizotinib (Xalkori®, Pfizer) was approved in the United States on the basis of results of a single-arm study of 50 patients (Shaw et al. 2014). The majority of patients had received some prior therapy for the treatment of NSCLC, although 14% were reported to be treatment naïve. Almost all patients had ROS1 fusions identified using a fluorescence in situ hybridization (FISH) assay from a tissue sample. The objective response rate (ORR) in this study was 72% (95% CI: 58%, 84%), with 3 complete responses and 33 partial responses. The median duration of response (DOR) was 17.6 months (95%

CI: 14.5, not reached), and the median progression-free survival (PFS) was 19.2 months (95% CI: 14.4 months, not reached) (Shaw et al. 2014).

Entrectinib (Rozlytrek™) was approved for ROS1-postive NSCLC in the United States based on the results in 53 adult patients across three clinical trials. Entrectinib is a potent inhibitor of the ROS1 tyrosine kinase with an IC50 of 0.2 nM (see Entrectinib Investigator's Brochure). In ROS1 fusion-positive NSCLC, patients treated with entrectinib had clinically meaningful and durable systemic responses. The majority of patients had received prior therapy for the treatment of their disease. The ORR was 77.4% (95% CI: 63.8, 87.7) with a median DOR of 24.6 months (95% CI: 11.4, 34.8). Patients with CNS metastases at baseline had an intracranial ORR of 55.0%, with 4 patients having a complete response (20.0%), and a median intracranial DOR of 12.6 months (Drilon et al. 2020).

Entrectinib has demonstrated clinical activity across multiple tumor types including colorectal, NSCLC, pancreatic, thyroid, breast, sarcoma, cholangiocarcinoma, mammary analogue secretory carcinoma (MASC), neuroendocrine tumors, and gynecological etiology in NTRK gene fusion-positive cancers (Demetri et al. 2018). Entrectinib was also approved in the United States for adults and pediatric patients 12 years of age and older who have solid tumors that harbor a NTRK gene fusion, based on the results across three clinical trials. As entrectinib is a potent inhibitor of both NTRK and ROS1 tyrosine kinase domains, it is hypothesized that therapeutic effects may be observed in patients who harbor ROS1 gene fusions, regardless of tumor type. Given that multiple tumor responses have been observed among different tumor types that harbor NTRK gene fusions, and the ability for entrectinib to cross the blood-brain barrier, entrectinib potentially presents a favorable option for patients whose tumors harbor ROS1 gene fusions outside of NSCLC.

1.1.2 Arm B: Inavolisib (GDC-0077) Treatment for Tumors with PI3Kalpha (PIK3CA) Activating Mutations

Phosphatidylinositol 3-kinase (PI3K) is a lipid kinase that upon activation by growth factor receptors and integrins regulates cell proliferation, survival, and migration. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP_2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP_3), a second messenger involved in the phosphorylation of AKT and other components in the AKT/mTOR pathway (Cantley 2002; Guertin and Sabatini 2007). PI3K and its downstream effectors, AKT and mTOR, are major nodes in the PI3K/AKT/mTOR signaling pathway and are critical for cell-cycle modulation, cell growth, metabolism, motility, and survival (Cantrell 2001; Hanahan and Weinberg 2011; Vanhaesebroeck et al. 2012).

Dysregulation of the PI3K/AKT/mTOR signaling pathway through multiple different mechanisms has been described in solid tumor malignancies, including activating and transforming mutations, as well as amplification, of PIK3CA – the gene that encodes the p110 alpha subunit of PI3K (Gustin et al. 2008; Yuan and Cantley 2008; Courtney et al.

2010). Activating mutations in the PIK3CA gene occur primarily in exons 9 and 20 ("hotspot" regions) that encode the helical and kinase domains of the alpha isoform of the PI3K protein (Bachman et al. 2004; Samuels et al. 2004). It is estimated that such activating mutations occur in ~11% of solid tumors (Roche, data on file).

Inavolisib (GDC-0077) is a potent selective inhibitor of the Class I PI3K alpha isoform, with $>$300-fold less potent biochemical inhibition for other Class I PI3Ks, including the beta, delta, and gamma isoforms, and increased activity in tumor cells bearing mutated PIK3CA over wild type (WT) PIK3CA cells. Inavolisib (GDC-0077) exerts its activity by binding to the ATP binding site of PI3K, thereby inhibiting the phosphorylation of membrane-bound PIP_2 to PIP_3. Inhibiting the phosphorylation of PIP_2 to PIP_3 decreases downstream activation of AKT and S6, resulting in decreased cellular proliferation, metabolism, and angiogenesis. Nonclinical studies demonstrate that inavolisib (GDC-0077) also induces specific degradation of mutated p110 alpha, inhibits proliferation and induces apoptosis of PIK3CA-mutation positive breast cancer cell lines, inhibits tumor growth in human breast xenograft models harboring PIK3CA mutations, and reduces downstream PI3K-pathway markers, including pAKT, pPRAS40, and pS6.

PI3K inhibition is an attractive target for clinical drug development because of the frequency of mutations observed across multiple tumor types in the PI3K-AKT-mTOR pathway (Massacesi 2016). Clinical trials, including SOLAR-1 (Phase III, alpelisib) and SANDPIPER (Phase III, taselisib), have demonstrated the anti-tumor activity of PI3Kα inhibitors in tumor types including estrogen receptor positive (ER+) breast cancers harboring PIK3CA mutations. More recently, a Phase I/Ib study of inavolisib (Study GO39374) has shown preliminary, encouraging safety and anti-tumor activity in PIK3CA–mutation-positive, hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) metastatic breast cancer.

With increasing evidence for the utility of PI3Kα inhibitors in tumors that harbor one or more PIK3CA mutations, further research of this drug class that includes patients whose tumors have one or more PIK3CA mutations is warranted.

1.1.3 Arm C: Alectinib Treatment for Tumors with ALK Gene Fusion

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is constitutively activated in some cancers due to gene alterations, including chromosomal rearrangements. Many different ALK fusion partners have been identified in a variety of tumor types including but not limited to lung cancer, Spitz tumors, inflammatory myofibroblastic tumors (IMT), thyroid cancer, digestive tract cancer, ovarian cancer, and renal cell carcinoma (Cao et al. 2019). The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling, which can contribute to increased cell proliferation and survival in tumors expressing these genes. ALK gene alterations are generally in a mutually exclusive relationship with mutations in EGFR or KRAS (Soda et al. 2007; Inamura et al. 2008, 2009; Wong et al. 2009), although EGFR mutations may develop as

a resistance mechanism after treatment with crizotinib, an inhibitor of ROS1 activation (Doebele et al. 2012).

While the ALK fusions have been observed in many tumor types, the prevalence of these translocations is approximately 5% in NSCLC versus only ~0.1%–0.2% in non-NSCLC solid tumors (Hartmaier et al. 2017; Ross et al. 2017; Foundation Medicine 2019). Consequently, ALK inhibitor development has been largely limited to NSCLC.

Crizotinib, was the first ALK inhibitor approved for ALK-positive NSCLC demonstrating improvement in PFS and ORR over chemotherapy; however, no difference in overall survival (OS) was noted between the two groups (Shaw et al. 2013, Solomon et al. 2014).

Next-generation ALK inhibitors were designed to overcome two major limitations of crizotinib treatment: the development of resistance because of secondary (e.g., gatekeeper) mutations (predominantly in ALK or occasionally in other genes, such as EGFR, cKIT, or KRAS) (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013) and CNS relapse (crizotinib has poor control of brain metastases compared to other sites). Thus next-generation ALK inhibitors may offer patients a better chance of prolonged remission and minimize the development of CNS metastases and the attendant comorbidity.

Alectinib (Alecensa®) is a small-molecule, highly selective, and potent oral next-generation ALK inhibitor with a benzo[b]carbazole scaffold. In enzyme inhibition assays performed in vitro, this compound has been shown to selectively inhibit ALK and RET. The compound also shows high anti-tumor activity both in vitro and in vivo against tumor cell lines with some type of somatic ALK gene mutation, including NSCLC and anaplastic large cell lymphoma lines harboring an ALK translocation and a neuroblastoma line harboring an amplified ALK gene. Alectinib shows good exposure in the brain, demonstrated in rodents, and is not a substrate of efflux transporters in the blood-brain barrier, such as P-gp, and therefore is able to distribute into and be retained within the CNS.

While ALK fusions are rare in tumors other than non-squamous NSCLC, in vivo studies and clinical case reports suggest that ALK inhibition could be an interesting treatment approach for such patients. Cases of clinical responses have also been reported with alectinib treatment in patients with various solid tumors including papillary renal cell carcinoma (Pal et al. 2018), metastatic inflammatory myofibroblastic tumors (Honda et al. 2019; Saiki et al. 2017), pancreatic ductal adenocarcinoma, squamous cell carcinoma (Huang et al. 2018; Mayesaya et al. 2017), and large cell neuroendocrine carcinoma (Shimizu et al. 2019). This promising clinical activity in non-NSCLC tumors supports further investigation in this population in which ALK oncogenic fusions are particularly rare.

1.1.4 Arm D: Ipatasertib Treatment for Tumors with AKT Gene Activating Mutations or PTEN Loss or Loss of Function

AKT is one of the most frequently activated protein kinases in human cancers, and plays a critical role in tumor growth, proliferation, metabolism, survival, and resistance to therapy (Bellacosa et al. 1995; Manning and Cantley 2007; Jiang and Liu 2008; Tokunaga et al. 2008; Robey and Hay 2009). AKT is encoded by three closely related gene isoforms in the mammalian genome, AKT1, AKT2 and AKT3. AKT is the central node of the PI3K/AKT/mTOR pathway, and is negatively regulated by the tumor suppressor PTEN, a phospholipid phosphatase that negatively regulates the activity of PI3K. Most commonly found alterations in solid and liquid tumors include the loss of PTEN, activating and transforming mutations in the p110α subunit of PI3K, deregulation of receptor tyrosine kinase signaling, and oncogenic Ras mutations. Alterations in AKT itself, including overexpression and amplification of individual AKT isoforms, as well as an E17K mutation in the PH domain of AKT1 that results in PI3K-independent membrane recruitment of AKT1, have been identified in a subset of human cancers (reviewed in Bellacosa et al. 2005; Brugge et al. 2007; Tokunaga et al. 2008). All of these mechanisms of pathway activation ultimately funnel through AKT as the central node that drives cell survival, growth, proliferation, angiogenesis, metabolism, and migration (Manning and Cantley 2007). The prevalence of AKT1/2/3 gene activating mutations or genomic alterations resulting in PTEN loss or loss of function has not been fully characterized, but may occur in ~13% of solid tumors (Roche, data on file).

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase AKT. Ipatasertib binds to the activated conformation of AKT and is ATP competitive. Ipatasertib binding inhibits the kinase activity of AKT and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012). In clinical tumor samples, robust AKT pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan et al. 2013).

In nonclinical models with high levels of phosphorylated AKT or PI3K/AKT pathway activity (i.e., PIK3CA mutation, PTEN alterations), sensitivity to ipatasertib has been observed across different tumor models (Lin et al. 2013).

Study PAM4743g was an open-label, Phase I, dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics (PK) of ipatasertib as a single agent in patients with refractory solid tumors (Saura et al. 2018). Fifty-two patients across multiple tumor types, including metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, chondrosarcoma, and ovarian cancer, were enrolled into respective tumor-specific cohorts regardless of mutation status. Across all dosing cohorts, 16 of 47 (34%) of patients had a best overall response of stable disease (SD) or incomplete response (IR). The anti-tumor activity of single-agent ipatasertib in a patient

population whose tumors are AKT mutation positive or exhibit PTEN loss or loss of function is currently unknown.

Additionally, in a Phase II randomized, placebo-controlled study, ipatasertib plus paclitaxel as first-line therapy demonstrated improved PFS in patients with locally advanced or metastatic triple negative adenocarcinoma of the breast (TNBC) compared to paclitaxel alone (Kim et al. 2017). In the ipatasertib group, median PFS was 6.2 months (95% CI 3.8–9) versus 4.9 months (95% CI 3.6–5.4) with placebo (hazard ratio [HR] 0.6, 95% CI 0.37–0.98; p=0.037). In a subset of the study population, patients with PTEN-low tumors by immunohistochemistry [IHC] had a median PFS of 6.2 months (95% CI 3.6–9.1) with ipatasertib versus 3.7 months (95% CI), median PFS was 6.2 months (95% CI 3.6–9.1) with ipatasertib versus 3.7 months with placebo (HR 0.59, 95% CI 0.26–1.32; p=0.18). These promising results support further investigation in patients with tumors harboring activating AKT1/2/3 gene activating mutations or genomic alterations resulating in PTEN loss or loss of function alterations.

Based on the scientific rationale that PI3K/AKT/mTOR blockade reduces survival signals and acceptable safety profile observed to date, treating patients with solid tumors that harbor such alterations with ipatasertib warrants further investigation.

1.1.5 Arm E: Atezolizumab plus Chemotherapy for Tumors with Tumor Mutational Burden≥10/Microsatellite Instability High /Deficient Mismatch Repair

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, programmed cell death protein 1 (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). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

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.

In recent years, PD-L1/PD-1 inhibitors have demonstrated clinical efficacy in patients with advanced malignancies who have failed standard of care therapy and agents have shown activity across a broad range of tumor types. For example, in patients treated with atezolizumab, objective responses have been across a broad range of tumor types, including 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). Additionally, pembrolizumab has been approved in a tumor-agnostic setting based on mismatch repair deficiency (dMMR) or microsatellite instability high (MSI-H) as well as TMB $\geq$10 mutations per megabase.

A growing body of evidence points to higher TMB and MSI-H/dMMR being correlated with better clinical outcomes with checkpoint inhibitor therapies. The higher mutational burden in these tumors likely produces an array of immunogenic neoantigens that renders greater sensitivity to the effects of the immune system (Schumacher and Schreiber 2015). Evidence in a variety of cancer types suggests that patients with a high burden of somatic mutations derive significant clinical benefit from anti-PD1/PD-L1 therapy. Multiple clinical studies have reported that high TMB is associated with response to several immunotherapeutic agents, including anti- CTLA-4 in melanoma (Snyder et al. 2014; Johnson et al. 2016), anti–PD-L1 therapy in bladder cancer (Rosenberg et al. 2016), and anti–PD-1 therapy in lung and colorectal cancers (Le et al. 2015; Rizvi et al. 2015; Fehrenbacher et al. 2016). In a Phase II signal-seeking study, patients with advanced solid tumors who had progressed on or were intolerant to standard therapy, were treated with pembrolizumab. The ORR was 30.3% in patients with tissue TMB elevated tumors compared with 6.7% in patients with non-high TMB (Marabelle et al. 2019).

Combining immunotherapy with chemotherapy has been demonstrated to have a synergistic effect and enhance antitumor immunity and improve outcomes beyond those achieved with each therapy alone. It is thought that tumor cell killing by cytotoxic chemotherapy may expose the immune system to increased levels of tumor antigens, and unblocking tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in synergistic activity. Anti–PD-L1/PD-1 therapies have been approved in the United States across a broad range of indications including in combination with taxane or fluorpyrimidine chemotherapies. Given the promising activity of checkpoint inhibition in MSI-H/dMMR and TMB-H tumors and the synergistic effects and acceptable safety profile observed in combination with chemotherapy, further study of atezolizumab in combination with docetaxel, paclitaxel, or capecitabine is warranted in a tumor-agnostic setting.

1.1.6 HER2 Targeted Therapy for HER2-Positive Tumors

The ERBB2 gene, which encodes HER2, a member of the erbB family of receptor tyrosine kinases, has been described as a key proto-oncogene in solid tumors (Slamon et al. 1989; Slamon et al. 1987). Approximately 6% of all solid tumor samples tested at Foundation Medicine have demonstrated amplification or activating alterations in HER2 (Foundation Medicine database, Q1 2020). Until recently, development of HER2-targeted therapies has been focused in HER2-overexpessing tumors, with approved indications in breast and gastric cancers. More recently, there has been interest in the potential oncogenic effect of HER2 somatic mutations and targeting of HER2-mutation positive tumors (Bose et al. 2013; Cousin et al. 2018; Li et al. 2015).

HER2 activating mutations including insertions/deletions and point mutations in the kinase, transmembrane, and extracellular domains occur across solid tumors and have been identified as oncogenic drivers (Connell & Doherty 2017; Cousin et al. 2018; Wen et al. 2015). HER2 mutations occur at a prevalence of 1.48% in solid tumors (Hartmaier et al. 2017; Foundation Medicine 2019), and the majority of tumors do not have co-occurring HER2 mutations and HER2 amplification. HER2 mutations occur in as many as 10% of bladder cancers and at meaningful frequencies in more common tumors including lung, breast, gastric and colorectal cancers, among many others.

Nonclinical studies have demonstrated activity of HER2-targeted therapies in HER2 mutation-positive solid tumors including of neratinib, afatinib, dacomitinib, and trastuzumab in HER2 mutation-positive lung and breast cancer cell lines (Engelman et al. 2007; Greulich et al. 2012; Lee et al. 2006; Li et al. 2008; Shimamura et al. 2006; Wang et al. 2006). Nonclinical models have shown the inhibitory effects of single-agent trastuzumab on HER2 mutation-positive lung cancer cell lines (Greulich et al. 2012; Wang et al. 2006) and clinical series of patients with HER2 mutation-positive lung cancer have reported high response rates from trastuzumab-based therapy (Cappuzzo et al. 2006; Mazieres et al. 2013).

In the clinical setting, responses have been seen in patients with HER2 mutation-positive solid tumors who were treated with HER2-targeting therapies including epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors (summarized in Connell and Doherty 2017) and trastuzumab emtansine (Li et al. 2018). An ORR of 44% was observed in patients with HER2 mutation-positive lung cancers treated with trastuzumab emtansine (Li et al 2018).

Activating HER2 mutations have demonstrated increased tumorgenicity, invasiveness and survival compared with non-HER2 amplified cells (Wang et al. 2006; Bose et al. 2013). HER2 amplification and activating mutations occur across tumor types and nonclinical and clinical evidence suggests that tumors that harbor these alterations may be vulnerable to HER2-targeted therapy. This evidence, combined with the relatively low prevalence of HER2 alterations outside of breast, supports further assessment of the efficacy of HER2-targeted therapies in a tumor-agnostic fashion.

1.1.6.1 Arm F: Trastuzumab Emtansine plus Atezolizumab for HER2-Positive Tumors (without knownTMB-H/MSI-H/dMMR)

Trastuzumab emtansine (known as ado-trastuzumab emtansine in the United States) is a novel antibody-drug conjugate (ADC), specifically designed for the treatment of HER2-positive cancer. It is composed of the following components: trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an anti-microtubule agent derived from maytansine; and succinimidyl 4[-Nmaleimidomethyl] cyclohexane-1-carboxylate (SMCC), a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine binds to HER2 with an affinity similar to that of unconjugated trastuzumab. It is hypothesized that after binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca- alkaloids. It is thought that trastuzumab emtansine provides a dual mechanism of action providing both HER2 targeted inhibition from the trastuzumab component along with chemotherapy from DM1.

Trastuzumab Emtansine (T-DM1) therapeutic activity may be accentuated by enhancing anti-tumor immunity. Recently, it was shown that the precursor of DM1, ansamitocin P3 may potentiate antitumor immunity by inducing maturation of dendritic cells, facilitating antigen uptake and the migration of tumor-resident dendritic cells to tumor-draining lymph nodes (Martin et al. 2014; Müller et al. 2014). A HER2-positive murine model has suggested therapeutic efficacy was dependent on T-DM1 induced infiltration by effector T-cells. After T-DM1 treatment, tumors became more T-cell–inflamed with an increase in γδT-cells that may cooperate with cancer immunotherapy, natural killer (NK)-cells and expansion of CD45+ cells. In addition, paired samples from 28 HER2-positive breast cancer patients treated with T-DM1 prior to surgery demonstrated increases in tumor-infiltrating T-cells after treatment (Müller et al. 2015).

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.

Evidence suggests that treatment with atezolizumab plus an anti-HER2 therapy could have greater anti-cancer activity than either agent alone. Nonclinical studies have shown that trastuzumab inhibition of HER2-positive tumors could upregulate PD-L1, suggesting that trastuzumab and anti-PD-L1 therapy could be more effective against HER2-positive tumors than trastuzumab alone (Chaganty et al 2018).

Superior effectiveness of treatment with T-DM1 plus atezolizumab is also suggested by data from clinical studies. In the KATE2 trial, T-DM1 plus atezolizumab was compared to T-DM1 alone in the treatment of HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane. In the final safety and clinical activity analysis, overall survival was numerically greater in the T-DM1 plus atezolizumab arm over the T-DM1 only arm (stratified HR=0.74; 95% CI: 0.42–1.30) (Emens et al. 2019). This suggests that T-DM1 plus atezolizumab alone could have greater anti-tumor activity than T-DM1 alone. Furthermore, in KATE2, the safety profile of the combination was consistent with the known safety profile of each drug, suggesting tolerability for the combination (see treatment-specific appendix for more on risks and adverse event management of the treatment combination).

The presence of TMB-H and/or MSI-H/dMMR status is known to enhance the activity of anti-PD-L1/PD-1 targeting agents, but the impact of these biomarkers on the combination of T-DM1 plus atezolizumab is not yet well characterized. However, the body of available data suggests that there may be therapeutic benefit to the addition of atezolizumab to T-DM1, even in the absence of TMB-H and/or MSI-H/dMMR status. With these considerations, and taking into account the acceptable safety profile demonstrated in the KATE2 trial, further study of the combination in a tumor-agnostic setting is warranted.

1.1.6.2 Arms G & H: PH FDC SC with or without Chemotherapy for HER2-Positive Tumors

The fixed dose combination of pertuzumab and trastuzumab administered subcutaneously (PH FDC SC) represents a combination of both anti-HER2 monoclonal antibodies along with hyaluronidase in a single drug product and is approved in the United States for the treatment of HER2 positive early stage and metastatic breast cancer in combination with chemotherapy.

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signaling pathways, mitogen-activated protein (MAP) kinase and PI3K. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively.

Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated cell proliferation and PI3K signaling pathway in human tumor cells that overexpress HER2.

Both pertuzumab and trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) have been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Clinically, dual HER2 inhibition with both pertuzumab and trastuzumab has demonstrated superiority over regimens containing trastuzumab alone.

Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan, a polysaccharide found in the extracellular matrix of the subcutaneous tissue. In the doses administered, hyaluronidase in PH FDC SC acts transiently and locally.

The safety profile for HER2 inhibition in combination with docetaxel, paclitaxel, or capecitabine chemotherapy is known to be acceptable. Trastuzumab and pertuzumab are approved for use in combination with either docetaxel or paclitaxel in HER2 positive early stage and metastatic breast cancer and trastuzumab is further approved in combination with a regimen containing capecitabine in HER2 positive metastatic gastric cancer.

As noted above, HER2 amplification and activating mutations occur across tumor types and nonclinical and clinical evidence suggests that tumors that harbor these alterations may be vulnerable to HER2-targeted therapy. The wealth of efficacy and safety data supporting HER2 inhibition with or without chemotherapy, along with the relatively low prevalence of HER2 alterations outside of breast, supports further assessment of the efficacy of dual HER2-targeted therapies with or without docetaxel, paclitaxel, or capecitabine chemotherapy in a tumor-agnostic fashion.

1.1.6.3 Arm I: Trastuzumab Emtansine plus Tucatinib for HER2-Positive Tumors

Trastuzumab emtansine (known as ado-trastuzumab emtansine in the United States) is a novel ADC, specifically designed for the treatment of HER2-positive cancer. It is composed of the following components: trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an ant-microtubule agent derived from maytansine; and SMCC, a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine binds to HER2 with an affinity similar to that of unconjugated trastuzumab. It is hypothesized that after binding to HER2, trastuzumab- emtansine undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca alkaloids. It is thought that trastuzumab emtansine provides a dual mechanism of action providing both HER2 targeted inhibition from the trastuzumab component along with chemotherapy from DM1.

Tucatinib is a kinase inhibitor approved in the US in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer with or without brain metastases who have received one or more prior anti-HER2-based regimens in the metastatic setting. Tucatinib prevents phosphorylation of the tyrosine kinase domain of the HER2 receptor, preventing activation of MAPK and PI3K-AKT signal transduction pathways, thereby inhibiting tumor

cell proliferation, survival, and metastasis. In addition to the approved indication in breast cancer, preclinical data show activity of tucatinib in a variety of tumor type models as a single agent and in combination with other HER2-targeting agents and chemotherapy (Peterson et al, 2020).

The combination of trastuzumab emtansine and tucatinib was examined in a Phase 1b study of 57 HER2 positive breast cancer patients (Borges et al, 2018). The combination demonstrated an acceptable safety profile at doses of 3.6mg/kg for trastuzumab emtansine every 21 days and 300 mg for tucatinib twice per day. Additionally, promising anti-tumor activity was observed with a response rate of 48%.

The available clinical and preclinical data support the continued investigation of a dual inhibition approach in HER2 positive cancers beyond breast cancer. The combination of trastuzumab emtansine and tucatinib represents a unique opportunity to study the safety and efficacy of dual targeting of HER2 with an ADC and kinase inhibitor in a tumor-agnostic setting.

1.1.6.4 Arm J: Trastuzumab Emtansine plus Atezolizumab for HER2-Positive and TMB-H/MSI-H/dMMR Tumors

Trastuzumab emtansine (known as ado-trastuzumab emtansine in the United States) is a novel ADC, specifically designed for the treatment of HER2-positive cancer. It is composed of the following components: trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an ant-microtubule agent derived from maytansine; and SMCC, a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine binds to HER2 with an affinity similar to that of unconjugated trastuzumab. It is hypothesized that after binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca-alkaloids. It is thought that trastuzumab emtansine provides a dual mechanism of action providing both HER2 targeted inhibition from the trastuzumab component along with chemotherapy from DM1. Overall response rates in patients with NSCLC whose tumors contain HER2 amplification, HER2 mutation, and HER2 mutation plus amplification have been reported to be similar (approximately 50%) when treated with trastuzumab emtansine (Li et al. 2020).

Trastuzumab Emtansine (T-DM1) therapeutic activity may be accentuated by enhancing anti-tumor immunity. Recently, it was shown that the precursor of DM1, Ansamitocin P3 may potentiate antitumor immunity by inducing maturation of dendritic cells, facilitating antigen uptake and the migration of tumor-resident dendritic cells to tumor-draining lymph nodes (Martin et al. 2014; Müller et al. 2014). A HER2-positive murine model has suggested therapeutic efficacy was dependent on T-DM1 induced infiltration by effector T-cells. After T-DM1 treatment, tumors became more T-cell–inflamed with an increase in γδT-cells that may cooperate with cancer immunotherapy, NK-cells, and expansion of CD45+ cells. In addition, paired samples from 28 HER2-positive breast cancer patients

treated with T-DM1 prior to surgery demonstrated increases in tumor-infiltrating T-cells after treatment (Müller et al. 2015).

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.

Evidence suggests that treatment with atezolizumab plus an anti-HER2 therapy could have greater anti-cancer activity than either agent alone. Nonclinical studies have shown that trastuzumab inhibition of HER2-positive tumors could upregulate PD-L1, suggesting that trastuzumab and anti-PD-L1 therapy could be more effective against HER2-positive tumors than trastuzumab alone (Chaganty et al. 2018).

In the KATE2 trial, the addition of atezolizumab to T-DM1 did not demonstrate a meaningful PFS benefit in the intent-to-treat (ITT) population; however, an exploratory analysis suggested a PFS benefit for the combination in the PD-L1+ (PD-L1 IC $\geq$1%) subgroup (HR, 0.60 [95% CI: 0.32, 1.11]) [L. Emens et al, SABCS 2018]. Additionally, at the second planned interim OS analysis, although the number of OS events were small, the results suggested an OS benefit with atezolizumab plus T-DM1 in the PD-L1 immune cells positive (IC+) subgroup (1-year survival rate of 94% vs 88%) (Emens et al. 2019). While the magnitude of the benefit is uncertain given the limited number of patients in this subgroup, and the corresponding wide confidence intervals, these results suggest that T-DM1 plus atezolizumab could have greater anti-tumor activity than T-DM1 alone in patients with PD-L1+ (PD-L1 IC $\geq$ 1%) metastatic breast cancer. The incidence of Grade 3 to 5 adverse events was generally similar between the 2 arms. Overall, the safety profile of the combination was consistent with what is already known about the individual drugs, with no new safety signals, suggesting tolerability for the combination (see treatment-specific appendix for more on risks and adverse event management of the treatment combination).

The presence of TMB-H and/or MSI-H/dMMR status is known to enhance the activity of anti-PD1/PD-L1 targeting agents, but the impact of these biomarkers on the combination of T-DM1 plus atezolizumab is not yet well characterized. The occurrence of dual positive biomarkers across tumor types is known to be low (Roche internal analysis) and therefore, taking into account the acceptable safety profile demonstrated in the KATE2 trial, a tumor-agnostic approach to further investigate the combination of these agents is warranted in this study.

1.1.7 Arms K and L: Ipatasertib Plus Atezolizumab for PI3K Activating Mutations or AKT Activating Mutation and/or PTEN Loss/Loss of Function

AKT is the central node of the PI3K-Akt-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 through activating mutations in AKT1 (Carpten et al. 2007).

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. Blockade of the pathway has shown to be effective in many cancer types.

Ipatasertib (GDC-0068) is a novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt and the mechanism of action and rationale for use as a single agent is described in Section 1.1.4. 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.

The combination of ipatasertib and atezolizumab in tumors driven by activation of the Akt/PI3K pathway has the potential to provide therapeutic benefit by simultaneously addressing multiple nodes in the cancer immunity cycle (Chen and Mellman 2013), including release of cancer antigens via cancer cell death and recognition by T-cells. Additionally, preliminary evidence suggests that inihibtion of the Akt/PI3K pathway may modulate the immune microenvironment, reducing regulatory T-cells and increasing the trafficking of CD8 positive effector T-cells into the tumor microenvironment (Lopez et al. 2020b), potentially further supporting cancer immunity.

There are several clinical trials investigating combinations of ipatasertib and atezolizumab which include an ongoing Phase Ib in metastatic hormone-receptor-positive, HER-negative breast cancer (CO39611), metastatic TNBC (CO40115) and NSCLC (BO39610). On the basis of these results, combination treatment with these two agents can be safely investigated and is expected to have promising therapeutic potential in solid tumors.

1.1.8 Arm M: Ipatasertib Plus Paclitaxel for Co-mutations in the PI3K/AKT Pathway

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

Genes that encode intracellular signaling proteins of the PI3K/AKT pathway are some of the most commonly mutated genes in tumor cells. Whereas PI3K inhibitors can modulate PIK3CA mutation-driven activation of the pathway, mutations in additional genes for this pathway (e.g. PTEN or AKT) may lead to worse prognosis and resistance to PI3K targeted therapies (Jhaveri et al. 2021). Pharmacologic modulation of this pathway downstream of PI3K may provide a more effective treatment alternative for patients whose tumors harbor PIK3CA/PTEN or PIK3CA/AKT co-mutations.

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

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase Akt. Ipatasertib binds to the activated conformation of Akt and is ATP competitive. Ipatasertib binding inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G_1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012). In clinical tumor samples, robust Akt pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan et al. 2013).

There are several clinical trials investigating combinations of ipatasertib and paclitaxel including a Phase Ib study in HER2-negative breast cancer (STUDY PAM4983g, Arm C), a randomized Phase II (GO29227, LOTUS) comparing ipatasertib + paclitaxel versus

placebo + paclitaxel as first-line treatment for patients with inoperable locally advanced or metastatic TNBC and a randomized Phase III (CO40016) comparing ipatasertib + paclitaxel versus placebo + paclitaxel in patients with PIK3CA/AKT1/PTEN-altered tumors. In GO29227, results from this study showed improvement in PFS in the intent-to-treat (ITT) population (hazard ratio = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm) and more pronounced in the pre-specified patient population with PIK3CA/AKT1/PTEN-altered tumors (hazard ratio = 0.44; 9 months vs 4.9 months).

On the basis of these results, combination treatment with ipatasertib and paclitaxel in tumors with co-mutations of PIK3CA and AKT or PIK3CA and PTEN-alteration status can be safely investigated and has the potential to offer therapeutic benefit in solid tumors driven by activation of this pathway.

1.1.9 Arm N: Tiragolumab Plus Atezolizumab for TMB-H/MSI-H/dMMR Tumors

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel immune inhibitory receptor that is a member of the Ig super family (Yu et al. 2009; Manieri et al. 2017). TIGIT is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as the poliovirus receptor [PVR]) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014).

TIGIT expression is elevated in the tumor microenvironment in many human tumors, is coordinately expressed with other checkpoint immune receptors such as programmed death−1 (PD-1), and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017). Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with TIGIT−PVR interaction may enhance the magnitude and quality of the tumor-specific T-cell responses by means of increased expansion of T cells as well as improved T-cell priming and/or effector function.

PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1, described in detail in Section 1.1.5. 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)

Because TIGIT and PD-1 are coordinately expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathways may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab.

In preclinical models, concomitant blockade of TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. In one such preclinical model, tumor-infiltrating T cells demonstrate increased interferon (IFN)-γ expression (a hallmark of activation and anti-tumor activity of T cells) only when both TIGIT and PD-1 are blocked concurrently and not when each individual pathway is blocked by the respective single-agent treatment. Notably, co-inhibition of TIGIT and PD-L1 in this syngeneic tumor model was not associated with loss of body weight or any other observable adverse responses. On the basis of the results of these studies, it is hypothesized that the combination of an anti-TIGIT antibody with anti–PD-L1/PD-1 antibody may result in activation of anti-tumor immune responses leading to enhanced killing of T cells and improved clinical responses than with either agent alone.

Tiragolumab is a fully human IgG1/κ monoclonal antibody (MAb) that binds to TIGIT and prevents its interaction with PVR. Refer to the Tiragolumab Investigator's Brochure for details on nonclinical and clinical studies. 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. Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

In the primary analysis of the Phase II study GO40290 (CITYSCAPE) investigating atezolizumab in combination with tiragolumab or placebo, 48.7% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment in the ITT population. In the tumor proportion score (TPS) $\geq$ 50% population, 65.5% of patients in the tiragolumab plus atezolizumab group relative to 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

In all randomized patients with TPS $\geq$1% (n = 135), the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab group (16.2%); investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group (n = 67) relative to placebo plus atezolizumab (n = 68) group (stratified HR=0.57; 95% CI: 0.37 to 0.90; median PFS 5.4 vs. 3.6 months, respectively). Consistent with the Phase Ib portion of Study GO30103, the combination of tiragolumab with atezolizumab was well tolerated in the Phase II study.

Taken together with the growing evidence for TMB and MSI-H/dMMR being correlated with better clinical outcomes with checkpoint inhibitor therapies in general and the acceptable safety profile of tiragolumab plus atezolizumab observed to date, further

study of the combination is warranted in tumors with these biomarkers in a tumor agnostic setting.

1.1.10 Arm O: Pralsetinib for RET fusion positive Tumors

Increasing evidence implicates aberrant activation of the receptor tyrosine kinase RET (rearranged during transfection) as a critical driver of tumor growth and proliferation across a broad range of solid tumors (Mulligan 2014). RET, along with glial cell line-derived neurotrophic factors (GDNF) and GDNF family receptors-α (GFRα), normally mediates development, maturation, and maintenance of several neural, neuroendocrine, and genitourinary tissue types. Oncogenic RET activation occurs via gain-of-function mutations which constitutively activates RET, promoting ligand-independent tumor growth. Oncogenic RET activation was initially described in hereditary and sporadic thyroid cancers, and subsequently in NSCLC adenocarcinoma (Mulligan 2014). However, as next-generation DNA sequencing has become more prevalent, it has become apparent that oncogenic RET mutations occur in a variety of solid tumors.

1.1.10.1 RET-altered Thyroid Cancer

The main histologic types of thyroid cancer are localized differentiated thyroid cancer (DTC; ~90% of cases), medullary thyroid cancer (MTC; ~2% of cases) and anaplastic thyroid cancer ($<$ 1% of cases). DTC arises sporadically from thyroid follicular cells and consists of papillary thyroid cancer (~90%), follicular thyroid cancer (~5%), and Hürthle cell neoplasm (~2%) (NCCN 2020). In contrast, MTC arises from parafollicular C cells and occurs in both hereditary and sporadic forms. Oncogenic RET activation has been implicated as a driver for both DTC and MTC.

Gene rearrangements involving RET and a dimerization domain-encoding gene have been identified in ~10% of sporadic papillary tumors in adults, and in ~50%–80% of papillary tumors that occur after radiation exposure or arise in childhood. RET fusion alterations are more prevalent in radiation-exposed populations (Li et al. 2019). The dimerization domain provided by the fusion partner allows for constitutive association of RET kinase domains, leading to aberrant kinase activation that promotes tumorigenesis.

In December 2020, pralsetinib received accelerated approval from the FDA for the treatment of adults and pediatric patients $\geq$ 12 years of age with advanced or metastatic RET-mutated MTC who require systemic therapy, and adults and pediatric patients $\geq$ 12 years of age with advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and who are radioactive iodine (RAI)-refractory (if RAI is appropriate) (GAVRETO® [pralsetinib], U.S. Prescribing Information).

1.1.10.2 Other RET-driven Cancers

Emerging genomic and functional data implicate RET as a potential driver in several cancers beyond thyroid cancer and NSCLC (Borrello et al. 2013; Mulligan 2014). Upregulation of RET, GDNF, and/or GFRα has also been detected across solid tumor

indications, and this may promote RET activation, tumorigenesis, and drug resistance (Nakashima et al. 2007; Yang and Horten 2014; Platt et al. 2015). Thus, it is possible that other advanced solid tumors are dependent on RET activity and could respond to RET inhibition.

At present, it is unclear how much of the clinical efficacy associated with multikinase inhibitors (MKIs) is caused by RET inhibition, as MKIs do not inhibit RET completely. Furthermore, MKIs are associated with significant off-target toxicities. Thus, there is a need for precision therapies that provide durable clinical benefit by selectively targeting RET alterations and anticipated resistance mechanisms.

1.1.10.3 Pralsetinib Activity

Pralsetinib (previously known as BLU-667) is a potent and selective oral inhibitor of RET fusion proteins and oncogenic RET mutants. Pralsetinib shows potent antitumor activity in RET-driven tumor models, and demonstrates tolerability at pharmacologically active doses in non–clinical toxicology assays.

Study BLU-667-1101 (ARROW) is an ongoing Phase I/II study of pralsetinib in patients with thyroid cancer, NSCLC, and other advanced solid tumors. As of 13 February 2020, 11 of 13 response-evaluable patients with RET fusion-positive thyroid tumors had an objective response (ORR: 91% (95% CI: 59% to 100%) (Blueprint Medicines Corporation Press Release 2020). Amongst 48 NSCLC patients, 28 (58%) showed an objective response, while 100% experienced disease control. Of those, patients previously treated with platinum agents (n=35) showed a 60% objective response rate, while 5 of the 7 patients (71%) without prior treatment achieved confirmed partial responses. Pralsetinib once per day (QD) dosing at dose levels $\leq$ 400 mg demonstrated acceptable tolerability, as most adverse events were of low grade and reversible. For more details about the clinical safety of pralsetinib, please refer to the Pralsetinib Investigator's Brochure.

Adult patients with RET fusion-positive cancers other than thyroid cancer or NSCLC are poorly served by standard of care treatments, which have limited efficacy and/or significant off-target toxicity. Thus, there is a need for personalized therapies that selectively target RET alterations to provide lasting clinical benefit. Given the evidence of pralsetinib's clinical efficacy and the unmet medical need, pralsetinib has the potential to provide significant benefit to tumor-agnostic, RET positive adults. As pralsetinib is generally well tolerated with an acceptable safety profile, the benefit-risk assessment for this cohort is considered to be favorable.

1.2 STUDY RATIONALE

This Phase II, multicenter, non-randomized, open-label, multi-arm study will evaluate the efficacy and safety of several agents in patients with advanced unresectable or metastatic solid tumors. Treatment will be based on each patient's tumor biomarker profile, and the trial will aim to include a broad patient population, inclusive of demographic populations under-represented in traditional clinical trials and rare tumor types. This will, in turn, broaden patient access to personalized treatments for otherwise excluded clinical trial patient populations.

In order to ensure the study population is diverse in underrepresented groups in clinical research, including patients of color, special attention has been paid to the selection of eligibility criteria appropriate for consideration of more diverse enrollment while still ensuring safety. An analysis by self-identified race and ethnicity is included to explore differences in therapeutic responses and clinical outcomes by ancestral groups.

The study will focus on the following actionable biomarkers and the corresponding targeted agents as shown in Figure 1.

Table 2 provides estimated pan-tumor prevalence of specific biomarker and overlapping biomarker alterations (Foundation Medicine 2020).

Table 2 Estimated Pan-tumor Prevalence of Specified Biomarkers

Target or Immune Marker	Biomarker Classification	Pan-tumor Prevalence
ROS1	Fusion-positive (excluding NSCLC)	0.11%
PI3K	PIK3CA activating mutation(s)	11.2%
ALK	Fusion-positive (excluding NSCLC)	0.11%
AKT1/2/3	AKT-Activating mutation or PTEN-Loss (deletion)/LOF	12.6%
ERBB2 (HER2)	Activating mutation or amplification (excluding breast cancer)	4.9%
PD-L1	TMB ≥ 10 mut/Mb or MSI-H/dMMR	13.2%
ERBB2 (HER2) & CD274 (PD-L1)	ERBB2 Activating mutation or amplification & TMB ≥ 10 mut/Mb or MSI-H/dMMR	0.5%
AKT	Co-mutations in PIK3CA and PTEN Co-mutation in PIK3CA and AKT	1.4% 0.09%
PD-L1 & TIGIT	TMB ≥ 10 mut/Mb or MSI-H/dMMR	13.2%
RET	Fusion-positive (excluding NSCLC, thyroid cancer)	0.48%

ALK= anaplastic lymphoma kinase; dMMR= deficient mismatch repair; HER2= human epidermal growth factor receptor 2; LOF= loss-of-function; Mb=Megabase; MSI-H= microsatellite instability high; mut=mutations; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; RET= Rearranged during Transfection; TIGIT=T-cell immunoreceptor with Ig and ITIM domains; TMB=tumor mutational burden.

1.3 RISK/BENEFIT ASSESSMENT

The conventional tumor histology-specific approach to drug development is not always appropriate in the era of precision oncology. For therapies targeting rare genomic alterations that are observed across a variety of tumors, enrolling a large, randomized study for each alteration or biomarker in individual tumor types is not feasible because of the significant amount of time required to identify a sufficient number of eligible patients. New clinical trial designs, including basket and umbrella studies, have been developed to overcome these barriers and provide for more efficient development of targeted therapies. Recently, several basket trials have led to health authority approvals of pembrolizumab, larotrectinib, and entrectinib in tumor-agnostic indications.

While these trials and subsequent approvals represent important steps towards personalized oncology treatment, many patients still have no targeted therapy options. Approximately 75% of oncologists report using next generation sequencing (NGS) testing to guide treatment decisions (Barroso-Sousa et al. 2019; Freedman et al. 2018). Despite this, only 26.8% of oncologists responded that NGS test results often informed treatment recommendations (Freedman et al. 2018), substantiating the need for additional drug and diagnostic development for widespread use of precision medicines and more personalized healthcare to become a reality. Of note, in an international survey, the barrier most frequently reported by oncologists was the inability to find a suitable trial (Barroso-Sousa et al. 2019).

Patients considered for enrollment in this study will have advanced unresectable or metastatic solid tumors and their treating investigator must consider treatment in a clinical trial an appropriate option for their care. This will include patients for whom no current available standard therapy exists, or for whom therapies that will convey clinical benefit are not available and/or not suitable options per the treating physician's judgment.

Additionally, the respective safety plan for each arm has been designed to ensure patient safety by utilizing inclusion and exclusion criteria that are consistent with the known safety profiles of the investigational agents along with treatment-specific toxicity management guidelines. A Steering Committee composed of multidisciplinary members of Roche/Genentech and external experts will be set up to review safety data at periodic intervals in order to identify the emergence of new or increased safety signals.

1.3.1 Risk/Benefit Assessment during COVID-19

1.3.1.1 All Treatment Arms

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear whether or how cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19. It is not known whether any of the agents being investigated in this study will increase the risk of infection with SARS-CoV-2 (see Section 1.3.1.2) for additional information regarding atezolizumab). Patients with a serious infection requiring intravenous (IV) antibiotics within 4 weeks prior to initiation of study treatment or any active infection that, in the opinion of the investigator, could impact patient safety will be excluded from study participation, and patients will be carefully monitored for infections during the study.

1.3.1.2 Immunotherapy Treatment Arms (Arms containing Atezolizumab: E, F, J, K, L & N)

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

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

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

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic

features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

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 (SITC 2020).

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

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

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

Given the mechanism of action for atezolizumab and other combinations within the study (Arm E: atezolizumab and chemotherapy [docetaxel, paclitaxel and capecitabine], Arms F and J: atezolizumab with trastuzumab emtansine, Arms K and L; atezolizumab plus ipatasertib, and Arm N: atezolizumab with tiragolumab), immune mediated adverse events are potential overlapping toxicities and should be monitored closely by the investigator and site personnel.

For Arm E (atezolizumab plus chemotherapy), neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of multiple therapies that are selected based on potential predictive biomarkers identified in patients with solid tumors.

2.1 EFFICACY

2.1.1 Primary Efficacy Objective

The primary objective for this study is to evaluate the efficacy of various treatments and/or combinations of treatments in eligible patients with advanced unresectable or metastatic solid tumors, on the basis of the following endpoint:

- The primary endpoint for each arm of this study will be confirmed ORR (cORR) as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors [Wen et al. 2017]. The cORR is defined as the proportion of patients whose confirmed best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objectives for this study are to evaluate the efficacy of each targeted treatment on the basis of the following endpoints:

- PFS, defined as the time from start of treatment to the first occurrence of 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 objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- PFS rate at 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1.
- Disease control rate (DCR), defined as the proportion of patients *whose best response is confirmed CR, confirmed PR, or a response of CR, PR, SD, or non-CR/non-progressive disease (PD) for a minimum of 98 days for 28-day cycle arms or 70 days for 21-day cycle arms after the first treatment date*. DCR will be summarized in the same fashion as the primary efficacy endpoint except, for DCR we will limit analysis to the subgroup in the efficacy population consisting of those with measurable disease.

2.1.3 Exploratory Efficacy Objectives

Exploratory efficacy objectives are to evaluate efficacy based following the following:

- Analysis of primary and secondary efficacy endpoints when subgrouped by basket, tumor site of origin, and/or self-reported race and ethnicity.

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of the study medications for the tumor types studied based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted clinical laboratory test results

2.3 BIOMARKERS OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are early surrogates of efficacy or relapse, are associated with a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study drug(s), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- The association of baseline and changes in circulating tumor DNA (ctDNA) levels with response and progression to therapy.
- Determination of baseline and changes in expression or levels of biomarkers in the tumor tissue or blood that may be associated with response or resistance to therapy.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

MyTACTIC is a Phase II, multicenter, non-randomized, open-label, multi-arm study designed to evaluate the safety and efficacy of targeted therapies as single agents or in rational, specified combinations in patients with advanced unresectable or metastatic solid tumors determined to harbor specific biomarkers. Patients will be enrolled based on local testing performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic laboratory. For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

The multi-arm structure of the MyTACTIC study allows patients with solid tumors to be treated with a drug or drug regimen tailored to their biomarker identified at screening. Each study treatment arm may have separate endpoints, screening, and treatment requirements, defined in the respective appendix. Futility analyses will be employed on all treatment arms to limit enrollment where evidence of very limited or lack of efficacy is observed.

During the study, the following biomarker samples will be collected:

Tumor tissue

- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

Blood samples

- Mandatory blood samples will be collected at screening, 8 weeks after first treatment, and at disease progression *(within 7 days after progression)* for analyses including ctDNA

These samples will be used to evaluate predictive and/or prognostic biomarkers, including but not limited to biomarkers related to driver oncogene signaling, response to study treatment, tumor pathogenesis, and mechanisms of resistance.

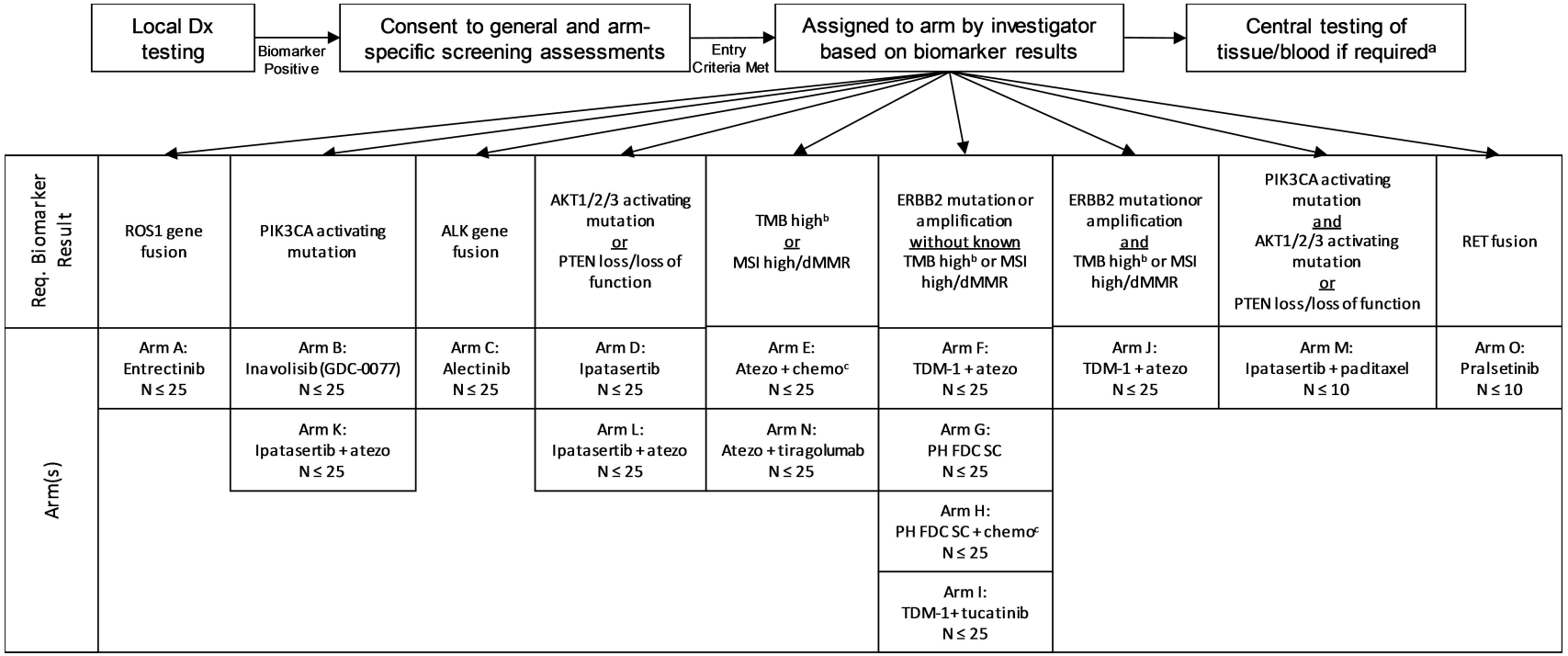
The requirements for tissue and blood samples for screening and standardized testing purposes are described in Section 4.5.7

Treatment will be assigned by the treating investigator on the basis of relevant specified biomarkers, and will continue until radiographic disease progression (per RECIST v1.1 [Eisenhauer et al. 2009]; RANO Criteria for primary CNS tumors [Wen et al. 2017]), or loss of clinical benefit for specific treatment arms with Medical Monitor consultation (see Section 3.1.2 for treatment beyond disease progression), unacceptable toxicity, patient or physician decision to discontinue, or death, whichever occurs first. If a patient discontinues treatment prior to disease progression (because of adverse event or other reason), tumor assessments will continue as specified in the treatment-specific appendix until disease progression, death, withdrawal of consent, or arm/study closure by the Sponsor, whichever occurs first.

Patients who do not meet the criteria for participation in this study (screen failure) or the timeline for the screening window may qualify for re-screening at the investigator's discretion. Patients must re-sign the consent form prior to rescreening. The investigator will record reasons for screen failure in the screening log.

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



atezo=atezolizumab; chemo=chemotherapy; dMMR=deficient mismatch repair; Dx=diagnosis; MSI=microsatellite instability; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; TDM−1=trastuzumab emtansine; FMI=Foundation Medicine, Inc.; MSI=microsatelite; Req=required; RET= Rearranged during Transfection; TMB=tumor mutational burden.

Note: If more than one biomarker is identified, the investigator will decide which treatment the patient will receive.

[a] For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

[b] TMB high is defined as ≥ 10 mutations per megabase.

[c] Investigator's choice of docetaxel, paclitaxel, or capecitabine.

Steering Committee

A Steering Committee will be formed of multidisciplinary members from Roche/Genentech, and external experts to provide clinical and methodological expertise to the oversight of the study. The Steering Committee will review data and provide consultation in evaluating efficacy and safety data for each study arm; and, subsequently, make recommendations regarding the eligibility of patients, appropriate treatment decision, statistical analyses, and clinical trial design. The committee will operate according to a pre-specified charter.

Safety will be reviewed by the Steering Committee to identify the emergence of new or increased safety signals. The Steering Committee will also review efficacy data and advise on an arm's continued accrual of patients with specific tumor types to targeted therapy at interim analyses. Genentech will consider the Steering Committee's recommendations in any decisions regarding the study conduct.

3.1.2 Dosing of Study Treatment beyond Disease Progression

In the absence of unacceptable toxicity, dosing of study treatment beyond radiographic disease progression may be permitted for patients in specific treatment arms upon consultation with the Medical Monitor, if evidence of persistent clinical benefit is determined by the investigator and documentation is provided to the Sponsor.

If the above criteria are met, dosing of study treatment will continue until unacceptable toxicity, loss of clinical benefit (as determined by the investigator), or withdrawal of patient consent. Loss of clinical benefit is defined as the following:

- Appearance of signs and symptoms (including worsening of laboratory values) indicating disease progression
- Decline in ECOG performance status due to disease progression
- Presence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g. cord compression) requiring alternative medical intervention

3.1.3 Number of Patients

Approximately 260 patients are anticipated to be enrolled at approximately 60 sites. Each arm will be limited to approximately 25 patients or 10 patients, as indicated in the Study Schema (Figure 1).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur approximately 1 year after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

This modular basket study has been designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or as part of rational combinations in patients with advanced unresectable or metastatic solid tumors determined to harbor specific biomarkers. Thus, patients are assigned to treatment arms based on the presence of tumor mutations or other biomarkers that are known or expected to be predictive of response and/or outcomes.

The patient population selected for this trial is based on the unmet medical need of patients with advanced solid tumors possessing rare oncogenic alterations that may be addressed by therapy targeted against these alterations. Current and potential future treatment arms involve biomarkers present across a variety of tumors.

Targeted or biomarker-driven therapy for patients has proven to be safer and more effective compared with conventional chemotherapy (Rosell et al. 2012; Solomon et al. 2014). While tissue testing is common for certain markers in some tumor types, a multitude of other potential targets have been identified for which testing may not routinely be performed. Further, a significant portion of patients never have their tumor tissue molecularly profiled and therefore may receive cytotoxic chemotherapy or supportive care only, depending on performance status and other clinical factors.

Many of the genomic alterations of interest are considered rare, making the ability to identify enough patients to conduct an adequate randomized trial very challenging, even within a tumor-agnostic umbrella trial design. Additionally, randomization would be challenging not only due to rarity of populations, but in the variability of standards of care between tumor types and even between lines of treatment within a tumor type. A single-arm, open-label design is optimal to demonstrate clinically relevant efficacy of a personalized biologically directed treatment, as compared with conventional chemotherapy or Phase I clinical trials, in the context of biomarker-selected rare-disease populations.

Rationale for the individual treatment arms are contained in the treatment-specific appendices.

3.3.1 Rationale for Biomarker Assessments

Cancer is a heterogeneous disease, but selection of patients based on the presence of oncodriver alterations allows for more specific targeting of the driver of disease. Within a given treatment arm, the genomic biomarkers under study in this trial may lead to variability of clinical responses among the different tumor types enrolled, based on relative differences in patient/prognostic factors, oncogenicity of individual alterations (e.g., fusion partner), and the presence or absence of intrinsic resistance mechanisms (Hartmaier et al. 2017). Therefore, patients may not benefit equally from study treatment in one or more of the study arms.

The goal is to study treatments based on the biomarkers present in a patient's tumor—agnostic to tumor type—and to ultimately determine the population(s) that benefit from targeted therapy based on biomarkers previously associated with clinical response. This may be fully tumor/tissue-agnostic or may represent a more limited patient population within a biomarker-defined indication.

A second goal is to better define the reason(s) for observed variations in clinical response to alteration-targeted agents among tumor types. Tissue and blood collected prior to dosing will be assessed in an effort to identify those patients with biomarker-driven pathogenesis who are most likely to respond to study treatment in the assigned study arm, as well as to study potential mechanisms of primary resistance where lack of or limited efficacy is observed. Biomarker samples will be collected at disease progression in an effort to monitor recurrence and to identify acquired resistance mechanisms to the assigned study treatment arm (blood is mandatory; tissue optional). Additionally, the sample(s) may be used for molecular testing.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately 260 patients with advanced unresectable or metastatic solid tumors with a positive biomarker result (per treatment arm-specific definitions) based on local testing results from a CLIA-certified or equivalently accredited diagnostic laboratory.

4.1.1 Inclusion Criteria

Patients must meet the following general inclusion criteria to be eligible to enroll in any treatment arm:

- Signed treatment-specific Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Positive biomarker results from a CLIA-certified or equivalently accredited diagnostic laboratory and availability of a full report of the testing results. This may be from a tissue or blood sample.
- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI: Sufficient archival tissue or a recent pretreatment tissue sample must be available for central testing (i.e. at least 11 slides or equivalent block) unless approved by Medical Monitor. If both archival and recent tissues are available, the recent tissue should be preferentially submitted. See Section 4.5.7 for full requirements.
- Participation in a clinical trial is an appropriate treatment option, in the opinion of the investigator
- Ability to comply with the study protocol

- Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic solid malignancy
- Evaluable or measurable disease (i.e., at least one target or non-target lesion per RECIST V1.1 or one measurable or non-measurable lesion per RANO criteria for patients with primary CNS tumors)
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2
- Life expectancy ≥ 8 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC per arm-specific eligibility criteria
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN), with the following exceptions:

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

    Patients with documented liver or bone involvement: ALP ≤ 5 × ULN
  - Total bilirubin ≤ 1.5 × ULN with the following exception:

    Patients with known Gilbert disease: total bilirubin ≤ 3 × ULN
  - Serum creatinine ≤ 1.5 mg/dL or Glomerular filtration rate > 50 mL/min/1.73 m^2 as calculated through use of the Chronic Kidney Disease Epidemiology Collaboration equation

    Glomerular filtration rate (GFR) estimation: GFR=141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] where:
    Scr is serum creatinine in mg/dL,
    κ is 0.7 for females and 0.9 for males,
    α is -0.329 for females and -0.411 for males,
    min indicates the minimum of Scr/κ or 1, and
    max indicates the maximum of Scr/κ or 1
  - Albumin ≥ 25 g/L (2.5 g/dL)
- Agrees to take measures to prevent pregnancy in the patient or partner (see Appendix 2 for details)
- In addition to the general inclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific inclusion criteria for the respective arm as detailed in the treatment-specific appendix (see Table 1 for list of treatments and appendices).

  Note: The requirements for enrollment into a specific arm may be more stringent.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be ineligible and excluded from study entry in any arm:

- Current participation or enrollment in another therapeutic clinical trial
- Eligible for an approved indication included in the local prescribing information for the applicable study treatment
- Symptomatic or actively progressing CNS metastases

  Asymptomatic patients with treated or untreated CNS metastases are eligible, provided that all of the following criteria are met:

  - No ongoing requirement for corticosteroids as therapy for CNS metastases, unless noted otherwise in the arm-specific appendix
  - No evidence of interim progression between the completion of CNS-directed therapy and screening radiographic study
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Evaluable disease must be present outside the CNS
- History of leptomeningeal disease, unless noted otherwise in the arm-specific appendix
- Wide field radiotherapy within 14 days prior to start of study treatment
- Stereotactic radiosurgery within 7 days prior to start of study treatment
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections, or any active infection that, in the opinion of the investigator, could impact patient safety
  - In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1; recovery of treatment-related toxicity consistent with other eligibility criteria
  - Androgen blockage may be continued for male patients with prostate cancer
- Patients known to be positive for HIV are excluded if they meet any of the following criteria:
  - CD4+ T-cell count of <350 cells/μL
  - Detectable HIV viral load
  - History of an opportunistic infection within the past 12 months
  - On stable antiretroviral therapy for <4 weeks

- Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exceptions:
  - Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
  - Patients with untreated HCV may be enrolled if the HCV is stable, the patient is not at risk for hepatic decompensation, and the intended treatment is not expected to exacerbate the HCV infection
  - Patients on concurrent HCV treatment may be enrolled if they have HCV below the limit of quantification
- Patients known to have active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test)
  - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA
- History of or concurrent serious medical condition or abnormality in clinical laboratory tests that, precludes the patient's safe participation in and completion of the study or confounds the ability to interpret data from the study (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
  - Patients with well-controlled comorbid disease on a stable treatment regimen for 4 weeks prior to screening are eligible for the study.
- History of malignancy other than disease under study within 3 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 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
- Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy of study treatment
- Major surgical procedure, other than for diagnosis, or significant traumatic injury within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or higher), myocardial infarction, or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmias, or unstable angina
- Pregnant or breastfeeding, or intending to become pregnant during the study
- In addition to the general exclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific exclusion criteria for the respective arm as detailed in the treatment-specific appendix (see Table 1 for list of treatments and appendices).

Note: The requirements for enrollment into a specific arm may be more stringent

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

All patients will be assigned to a specific treatment arm by the treating investigator based on the biomarker results of a qualifying assay.

An interactive voice- or web-based response system (IxRS) will be used to manage patient screening, enrollment, and tracking. Patients who are diagnostic positive for a treatment arm, meet the general and applicable treatment-specific eligibility criteria, and have provided arm-specific written informed consent will be registered via IxRS.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The study treatment arm designs are provided separately in the appendices.

Details of each study treatment, recommended concomitant medications, and prohibited medications are also contained in the treatment-specific appendices.

See Table 1 for a full list of treatment arms and the associated appendices.

4.3.1 Study Treatment Formulation and Packaging

Refer to the treatment-specific appendices for details.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in the treatment-specific appendices (see Table 1).

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

Patient compliance with self-administration of orally administered study treatment will be assessed by medication diary and standard pill counts. Patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in the treatment-specific appendices.

4.3.3 Investigational Medicinal Product Handling and Accountability

All investigational medicinal products (IMPs) required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel

or mobile nurse, if applicable]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMPs received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. 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. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor 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 accountability log.

Refer to the pharmacy manual and/or the study drug's Investigator's Brochure or local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Study Treatments

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMPs as listed in Table 1 or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing IMPs in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until 28 days after the last dose of study treatment. All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives or hormone-replacement therapy and do not have breast cancer may continue these medications under the supervision of their physician. Androgen blockage may be continued for male patients with prostate cancer. Other medications may be continued unless otherwise indicated in the specific study drug appendix.

Unless noted otherwise in the arm-specific appendix, palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain), is permitted provided it does not interfere with the assessment of tumor lesions (e.g., the lesion being irradiated is not a target lesion for response assessments, because that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1 or RANO [for patients with patients with primary CNS tumors]).

Supportive care, including antiemetic medications, may be administered at the discretion of the investigator. For details on regimen-specific concomitant therapy, prohibited food, and additional restrictions; please refer to the appropriate treatment arm-specific appendices (see Table 1 for full list of appendices).

4.5 STUDY ASSESSMENTS

The treatment-specific assessments and schedules of activities to be performed during the study are provided in the treatment-specific appendices (see Table 1).

All activities should 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 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.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment or as indicated in the schedule of activities. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. Demographic data for both enrolled and screen-failed patients, as well as reasons for screen failure (if applicable) will be captured in the IxRS.

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed 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 should be performed at each visit in accordance with standard clinical practice, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event) unless noted in the arm-specific Schedule of Activities.

4.5.5 ECOG Performance status

Performance status will be assessed according to Eastern Cooperative Oncology Group (ECOG) definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

4.5.6 Tumor and Response Evaluations

All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation according to the arm-specific schedule of assessments (see arm-specific appendices) until investigator-determined radiographic disease progression or loss of clinical benefit (in the case of treatment beyond disease progression in applicable arms), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first. 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 baseline. Tumor assessments must be performed independently of changes to the study treatment administration schedule (i.e., when treatment is withheld). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration on Day 1 of Cycle 1. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. Objective response (complete response or partial response) must be confirmed by repeat assessment at least 4 weeks after initially documented response.

Tumor assessments should be performed using the same modality as baseline throughout the course of treatment, unless contraindicated by evolving patient condition. Screening assessments must include computed tomography (CT) scans (with oral or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and head. Bone scan and CT scans of the neck should be performed if clinically indicated or if required as specified in the arm-specific appendices. In the event a positron emission tomography (PET)/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. Patients without brain or bone disease at baseline do not need brain or bone scans at subsequent tumor assessments unless clinically warranted or if required as specified in the arm-specific appendices. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same

contrast protocol for CT scans). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Response will be assessed by the investigator on the basis of physical examinations, CT scans, and MRI scans according to RECIST v1.1 (see Appendix 3) or RANO (see Appendix 4), if applicable. Assessments should be performed by the same evaluator to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Deidentified imaging data may also be used for exploratory research purposes including digital image analysis.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

In addition, treatment-specific laboratory assessments will be performed as described in the specific appendix for each study drug (See Table 1 for list of appendices).

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

- Hematology/CBC (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count)
- Chemistry panel (serum or plasma) (glucose, BUN, creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), ALP, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin)
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

- Blood samples for somatic tumor-specific genetic testing including ctDNA will be collected from all patients participating in the trial. These samples will be used for research purposes to identify biomarkers that correlate with treatment response or resistance and may be used for diagnostic assay development.
- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI: Archival or recently collected tumor tissue sample obtained prior to study treatment must be submitted within 21 days of enrollment for central testing, including exploratory research on biomarkers and biomarker assay development. In exceptional circumstances, enrollment may be allowed without sufficient tissue with Medical Monitor approval.
  - A representative formalin-fixed paraffin embedded (FFPE) tumor specimen (obtained prior to study treatment) in a paraffin block (preferred) or at least

11 slides containing unstained, freshly cut, serial sections should be submitted within 21 days of Cycle 1, Day 1. Tumor tissue should be of good quality based on total and viable tumor content. Samples collected via core-needle biopsy (at least three cores, embedded into a single paraffin block), or any other resection/excisional means are acceptable. Fine needle aspiration (FNA), cytology, or cell pellets from ascites/pleural effusions/lavage samples are acceptable with sufficient cellularity to meet tumor content requirements. Tumor tissue from bone metastases that are subject to decalcification is not acceptable.

Exploratory research on patient tissue or blood samples may involve extraction and/or analysis of DNA, cell-free DNA, RNA or proteins for the purposes of addressing questions related to biological mechanisms of treatment response and/or resistance, oncogenesis and tumor immunity. Genomic testing may include targeted, whole exome and/or whole genome testing methods for assessment of somatic or germline sequence variations. Analysis of gene expression may be tested using RNA and protein expression methods such as, but not limited to RNA next generation sequencing and immunohistochemistry.

Screening tumor tissue and blood samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Central NGS analysis may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain results through Foundation Medicine's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.8.3), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Blood and tissue samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first.

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

Data arising from sample analysis, including data on genomic variants, 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 (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Optional Samples for Research Biosample Repository

4.5.8.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 4.5.8) will not be applicable at that site.

4.5.8.3 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, diseases, or drug safety:

- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover 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 variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

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

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

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

4.5.8.4 Confidentiality

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

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

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

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

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

4.5.8.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.8.6 Withdrawal from the Research Biosample Repository

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

global.rcr-withdrawal@roche.com.

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

4.5.8.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, ARM AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients will return to the clinic for an End of Treatment visit at ≤28 days after last treatment. Patients must permanently discontinue study treatment if they experience any of the following:

- Disease progression, unless treatment beyond progression is allowed in the applicable arm
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

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

4.6.2 Patient Discontinuation from the Study

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

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event

- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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

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 Study Arm Discontinuation

The Sponsor has the right *to* close or restrict enrollment to a study arm at any time. Reasons for closing or restricting enrollment to a study arm 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 or a subset of patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to close any study arm.

4.6.5 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

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, if applicable, treatment interruption or discontinuation, are provided in the treatment-specific arms. Refer to Table 1 for treatment-specific appendices.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for infections prior to and during study participation should be performed according to local/institutional guidelines or those of applicable professional societies (e.g., ASCO/ESMO).

A Steering Committee composed of multidisciplinary members of Roche/Genentech and external experts will be set up to review safety data at periodic intervals in order to identify the emergence of new or increased safety signals.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE (v5.0); see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Please refer to the following treatment-specific appendices in Table 1 for additional adverse events of special interest relevant to the respective study treatment.

5.2.4 Selected Adverse Events

Additional data may be required to be collected for selected adverse events. Please refer to the treatment-specific appendices outlined in Table 1 for selected adverse events (where applicable) and their management.

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., discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drugs other than atezolizumab and until 90 days after the final dose of atezolizumab.

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 nondirective questions include the following:

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

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

5.3.3 Assessment of Severity of Adverse Events

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

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

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

NCI CTCAE (v5.0) = National Cancer Institute Common Terminology Criteria for Adverse Events.

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 4:

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

Table 4 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions or Injection-Site Reactions (When applicable)

For applicable study treatments, adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or

injection should be captured as a diagnosis (e.g., "infusion-related reaction" or "injection-site reaction" "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction or Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction or Injection Reaction eCRF. For patients receiving atezolizumab, there may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). In recognition of the challenges in clinically distinguishing between these two events, consolidated guidelines for medical management of IRRs and CRS are provided in the atezolizumab treatment-specific appendices.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory

abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of 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 drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The Steering Committee will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of 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 v 1.1, RANO (for primary CNS tumors). 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 drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

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

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

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

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the

event; see Section 5.4.2). For study treatments 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 study treatments, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional significant 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 patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators.

Emergency Medical Call Center Help Desk: 1 (855) 855-9112

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drugs other than atezolizumab and until 90 days after the final dose of atezolizumab. 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 Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment (or >90 days after the final dose of atezolizumab) are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

Table 5 Pregnancy Reporting Period after the Last Dose of Study Drug

	Timeframe after the Last Dose of Study Drug[a]	
Study Drug	Females	Males
Alectinib	90 days	90 days
Atezolizumab	5 months	Not applicable
Capecitabine	6 months	3 months
Docetaxel	6 months	3 months
Entrectinib	5 weeks	90 days
Inavolisib (GDC-0077)	60 days	98 days
Ipatasertib	28 days	28 days
Paclitaxel	6 months	3 months
PH FDC SC	7 months	7 months
Pralsetinib	2 weeks	1 week
Tiragolumab	90 days	90 days
Trastuzumab emtansine	7 months	7 months
Tucatinib	1 week	1 week

[a] If patient is receiving a combination of study drugs, the reporting period should be whichever is longer.

Instructions regarding pregnancy and contraception are provided in Appendix 2.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within the timeframe specified in Table 5 after the final dose of study drug. The investigator should

report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

Instructions regarding pregnancy and contraception are provided in Appendix 2.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

The female partner of a male patient exposed to study drug should be classified as a serious adverse event and recorded as described in paragraph above.

5.4.4 Reporting Requirements for Special Situations and Non-Serious Adverse Events Associated with a Special Situation

After initiation of study drug, special situations and adverse events associated with special situations will be reported until 28 days after the final dose of study drugs other than atezolizumab and until 90 days after the final dose of atezolizumab. Investigators should record all case details that can be gathered on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system within 30 calendar days of awareness. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drugs other than atezolizumab and 90 days after the final dose of atezolizumab), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

Drug	Document
Arm A: Entrectinib	Entrectinib Investigator's Brochure
Arm B: Inavolisib	Inavolisib (GDC-0077) Investigator's Brochure
Arm C: Alectinib	Alectinib Investigator's Brochure
Arm D: Ipatasertib	Ipatasertib Investigator's Brochure
Arm E: Atezolizumab plus chemotherapy	Atezolizumab Investigator's Brochure Docetaxel USPI Paclitaxel USPI Capecitabine USPI
Arm F: Trastuzumab emtansine plus atezolizumab	Trastuzumab emtansine Investigator's Brochure Atezolizumab Investigator's Brochure
Arm G: PH FDC SC	PH FDC SC Investigator's Brochure
Arm H: PH FDC SC plus chemotherapy	PH FDC SC Investigator's Brochure Docetaxel USPI Paclitaxel USPI Capecitabine USPI
Arm I: Trastuzumab emtansine plus tucatinib	Trastuzumab emtansine Investigator's Brochure Tucatinib USPI
Arm J: Trastuzumab emtansine plus atezolizumab	Trastuzumab emtansine Investigator's Brochure Atezolizumab Investigator's Brochure
Arm K: Ipatasertib plus atezolizumab	Ipatasertib Investigator's Brochure Atezolizumab Investigator's Brochure
Arm L: Ipatasertib plus atezolizumab	Ipatasertib Investigator's Brochure Atezolizumab Investigator's Brochure
Arm M: Ipatasertib plus paclitaxel	Ipatasertib Investigator's Brochure Paclitaxel USPI

Drug	Document
Arm N: Atezolizumab plus tiragolumab	Atezolizumab Investigator's Brochure Tiragolumab Investigator's Brochure
Arm O: Pralsetinib	Pralsetinib's Investigator 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

Details of criteria and statistical analyses will be provided in the Statistical Analysis Plan. The efficacy and safety analyses will be performed on the treated study population, which includes all enrolled patients who receive at least one dose of study medication.

Given this study consists of many single arms according to molecular alterations we will be estimating (providing confidence intervals and summary statistics) as opposed to formal statistical hypothesis testing.

6.1 DETERMINATION OF SAMPLE SIZE

The focus for this study will be estimation since the study is composed of many single arms specific to a targeted therapy. Estimation of the primary endpoint will be 95% confidence intervals using the Clopper-Pearson method. As such, the maximum margin of error for sample sizes 25, 50, and 75 are 20.7%, 14.5%, and 11.8%, respectively. On a per arm basis, if the lower bound of the confidence interval is larger than a benchmark specific to that arm, then we will consider the given treatment as a significant improvement over the benchmark.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuation from the study will be summarized by arm and, if applicable, by biomarker. The incidence of study treatment discontinuation for reasons other than disease progression will be tabulated similarly. Protocol deviations, including major deviations of inclusion/exclusion criteria, will be summarized in a similar manner by arm and, if applicable, biomarker.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, and medical history, including number of previous regimens) will be summarized using means, standard deviations, medians, and ranges for continuous

variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm in the efficacy population (same as safety population), which includes all patients with at least one dose of study treatment.

6.4 EFFICACY ANALYSES

The efficacy-evaluable population is defined as all enrolled patients who meet arm specific inclusion/exclusion criteria and have received at least one dose of study treatment.

6.4.1 Primary Efficacy Endpoint

The primary endpoint for this study will be cORR as assessed by the investigator and according to the corresponding assessment criteria (RECIST v1.1 or RANO). The cORR is defined as the proportion of patients whose confirmed best response is a CR or PR for those with measurable disease and CR for those with non-measurable disease. Confidence intervals at both 70% and 95% nominal levels will be reported using the Clopper-Pearson method. The primary efficacy endpoint will be computed for all treatment arms. If a patient receives at least one dose of study treatment and discontinues the study for any reason before confirmed response can be assessed, the patient will be considered a non-responder (not PR and not CR) and will be added to the denominator of the computation of cORR.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for each treatment arm will consist of DCR, PFS, and DOR, which are listed and defined below. All secondary endpoints will be computed for all treatment arms and will be computed on the efficacy evaluable population

- PFS, defined as the time from start of treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to the corresponding assessment criteria (RECIST v1.1 or RANO). The PFS will be estimated using the Kaplan-Meier method. Median PFS and 95% confidence interval will be computed using the Brookmeyer-Crowley method.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to the corresponding assessment criteria (RECIST v1.1 or RANO). The DOR will be estimated using the Kaplan-Meier method. Median DOR and 95% confidence interval will be computed using the Brookmeyer-Crowley method.
- PFS rate at 3 months and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1. PFS rates will be computed using the Kaplan-Meier method with 95% confidence intervals for each rate given by Greenwood's formula.

- DCR is defined as the proportion of patients *whose best response is confirmed CR, confirmed PR, or a response of CR, PR, SD, or non-CR/non-PD for a minimum of 98 days for 28-day cycle arms or 70 days for 21-day cycle arms after the first treatment date*. DCR will be summarized in the same fashion as the primary efficacy endpoint except, for DCR we will limit analysis to the subgroup in the efficacy population consisting of those with measurable disease.

6.5 EXPLORATORY EFFICACY

6.5.1 Exploratory Efficacy Objectives

Exploratory efficacy objectives are to evaluate efficacy when subgrouped by tumor site of origin, and/or self-reported race and ethnicity.

6.6 SAFETY ANALYSES

The safety analysis population will include all patients who received at least one dose of study drug. Safety will be assessed through summaries of exposure to study treatment, adverse events, and changes in laboratory test results. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the NCI CTCAE (v5.0). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. A shift table of selected laboratory tests will be used to summarize the baseline and maximum post baseline severity grade.

6.7 BIOMARKER ANALYSES

- For all treatment arms, descriptive statistics of biomarker data will include means medians, ranges, and standard deviations, as appropriate. For categorical analyses, frequency distributions will be tabulated as appropriate.
- Biomarker data in blood and tumor tissue and biomarker data collected over time (if available) will be used for additional subgroup analyses where primary and secondary efficacy endpoints and safety will be evaluated.

Although no formal statistical analysis of exploratory biomarkers will be performed, in an effort to understand the association of these markers with study treatment response, data may be analyzed in the context of this study and in aggregate with data from other studies. Results will be presented in a separate report.

6.8 NON-BINDING FUTILITY ANALYSES

For some arms, limited data are available regarding the efficacy and safety of the treatment across the eligible tumor population(s). Therefore, data from the first 12 efficacy-evaluable patients in a given arm will be used to conduct non-binding interim tumor agnostic futility analyses. Futility analyses for some arms may be conducted with the integration of data from other ongoing studies (see the Statistical Analysis Plan [SAP] for details). These analyses will be used to identify whether a treatment may be ineffective in a tumor agnostic population due to limited or lack of efficacy, and further accrual into such an arm may be stopped. Enrollment will not be stopped while awaiting results of the tumor agnostic futility analysis. To perform the analysis we will use Bayesian gating with arm-specific gating criteria and non-informative prior where futility will be declared if there is a posterior probability of greater than 60% that the true cORR is less than an arm-specific unacceptable level.

6.9 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization/Functional Service Provider (CRO/FSP) will be responsible for the 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other non-CRF data will be sent directly to the Sponsor and or the CRO, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction 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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered 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, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry

of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, images, 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 study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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 (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study treatment initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and

controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study treatment initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 60 sites will participate to enroll approximately 200 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., biomarker analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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.

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
MyTACTIC Biomarker Overview

Specific Tumor Gene Alterations		
Biomarker	**Allowed Alteration Types**	**Arms & excluded indications**
AKT1	Activating Mutations: E17K; L52R; Q79K, Other activating mutations with Medical Monitor approval	**Arm D**: Ipatasertib • Triple negative adenocarcinoma of the breast excluded **Arm L**: Ipatasertib plus atezolizumab **Arm M**: Ipatasertib plus paclitaxel • With PIK3CA co-mutation
AKT2	Activating Mutations: E17K Other activating mutations with Medical Monitor approval	
AKT3	Activating Mutations: E17K; L51R; Q78K Other activating mutations with Medical Monitor approval	
ALK	3' ALK fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain	**Arm C**: Alectinib • NSCLC excluded

Specific Tumor Gene Alterations		
Biomarker	**Allowed Alteration Types**	**Arms & excluded indications**
ERBB2 (HER2)	ERBB2 (HER2) gene amplification: NGS ≥6 copies/cell or ISH test: HER2:CEP17 ratio is ≥2.0 and the average HER2 copy/cell is ≥4.0 or Activating mutation: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S, S418T; A440T; P551L; R552S; S653C; V659E; G660D; R678Q; T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C Other ERBB2 (HER2) activating mutations with Medical Monitor approval	**Arm F**: Trastuzumab emtansine plus atezolizumab **Arm G**: PH FDC SC **Arm H**: PH FDC SC plus chemotherapy **Arm I**: Trastuzumab emtansine plus tucatinib **Arm J**: Trastuzumab Emtansine plus atezolizumab • With TMB-H / MSI-H/dMMR-positive tumors • Breast cancer excluded in all arms
PIK3CA	R88Q, G106A/D/R/S/V, K111N/R/E, G118D, N345D/H/I/K/S/T/Y, C420R, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, E545A/D/G/K/L/Q/R/V, Q546E/H/K/L/P/R, M1043I/T/V, H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S Other PIK3CA activating mutations with Medical Monitor approval	**Arm B**: Inavolisib (GDC-0077) • Primary CNS tumors excluded **Arm K**: Ipatasertib plus atezolizumab **Arm M:** Ipatasertib plus paclitaxel • with AKT1/2/3 or PTEN co-mutation

Specific Tumor Gene Alterations		
Biomarker	**Allowed Alteration Types**	**Arms & excluded indications**
PTEN	PTEN loss or loss of function is defined by any of the following criteria from a tissue-based NGS test: • PTEN homozygous deletion (copy number 0) • Presence of a PTEN gene dominant negative short variant (eg, C124S, G129E, R130X) • PTEN gene loss of heterozygosity (LOH) with copy number 1 without concomitant single-nucleotide variants • One deleterious short variant in the PTEN gene (described and/or listed below*) with a variant allele frequency ≥60% • One deleterious short variant in the PTEN gene (described and/or listed below*) with a concomitant loss of the non-mutant PTEN allele defined by loss of heterozygosity (LOH) with copy number 1, or LOH with copy number >1 PTEN loss is also defined as: • Biallelic PTEN gene loss by a validated in situ hybridization (ISH) test tested in a CLIA or equivalently certified laboratory. • PTEN protein loss by a validated immunohistochemistry (IHC) assay tested in a CLIA or equivalently certified laboratory. PTEN loss/LOF cannot be determined using a plasma ctDNA test for the purposes of this protocol. *Acceptable PTEN variants with variant allele frequency ≥60% or with concomitant loss of the non-mutant PTEN allele defined by LOH with copy number 1, or LOH with copy number >1: • Any protein-truncating mutations, including nonsense mutations and frameshift indels • Any mutation in the consensus splice donor and acceptor sequence that disrupts the consensus, including indels • Any missense or non-frameshift mutation that has been confirmed somatic as described in the COSMIC dataset or is in the list below* • Other applicable mutations with Medical Monitor approval	**Arm D**: Ipatasertib • Triple negative adenocarcinoma of the breast excluded **Arm L**: Ipatasertib plus atezolizumab **Arm M**: Ipatasertib plus paclitaxel • with PIK3CA co-mutation

Specific Tumor Gene Alterations		
Biomarker	**Allowed Alteration Types**	**Arms & excluded indications**
PTEN (cont.)	*A3S, K6E, K6I, K6N, S10N , K13E, K13del, R14G, R14M, R14_D22del, R15I, R15K, Y16C, D19N, G20E, F21S, I122S, L23F, L23V, D24E, D24G, D24N, D24X, D24_L25del, L25F, Y27C, Y27D, Y27S, I28M, N31H, N31K, I33S, I33del, A34D, M35R, M35V, G36E, G36R, G36V, L42P, G44D, R47G, D51del, D52N, V53G, V53del, V54L, R55G, R55S, R55_L70>S, F56V, L57S, L57W, D58Y, S59P, H61L, H61P, H61R, K62I, K62N, K62R, Y65C, Y65D, K66E, K66N, I67K, I67R, I67T, I67del, I67_Y68insY, Y68C, Y68H, Y68N, L70P, C71Y, E73V, H75N, H75_T78del, Y76del, A79T, K80E, K80N, F81C, N82T, A86P, A86V, Q87_P96del, Y88C, Y88H, F90L, F90S, E91A, E91Q, D92A, D92E, D92G, D92H, D92V, D92Y, H93D, H93Q, H93R, H93Y, N94I, P95L, P95S, P96L, P96Q, P96S, P96T, I101M, I101N, I101T, C105F, C105Y, C105G, C105R, C105S, D107Y, L108R, L108_D109del, W111R, L112P, L112V, V119F, A121E, A121P, A121_F145del, I122N, H123D, H123Y, C124R, C124S, C124Y, K125E, K125N, A126D, A126P, A126S, A126T, A126V, G127R, G127V, K128N, K128Q, G129E, G129R, G129V, R130E, R130G, R130L, R130P, R130Q, T131A, T131N, G132D, G132S, G132V, V133I, M134I, M134L, M134R, I135K, I135V, I135del, C136F, C136R, C136Y, Y138C, L139F, L140F, R142Q, K144I, F145I, F145_L146del, L146V, A148T, E150D, E150G, E150Q, A151T, L152P, L152R, L152V, D153E, D153N, D153Y, F154C, Y155C, Y155H, R159K, R159S, T160I, T160S, R161I, R161K, G165E, G165R, G165V, G165del, T167I, T167P, T167S, I168F, S170I, S170N, S170R, Q171E, Q171H, Q171K, Q171P, R173C, R173H, Y174D, Y174N, V175L, Y176del, Y177C, L182F, Y188S, L193P, L193del, M198K, M199del, P204S, P204T, M205I, P213R, F215S, V216M, V217A, V217I, Y225C, S227F, R234L, R234W, F241L, F241S, P244S, P246L, L247F, P248H, V249E, G251C, D252G, D252Y, I253N, V255A, V255G, E256K, M270I, F271S, H272Y, W274G, V275A, V275L, N276K, T277I, E284K, C304G, R308C, T319del, T319_K332del, E314K, N323K, L325P, L325R, D326G, D326_K342del, D331G, R335G, Y336F, S338T, P339L, F341V, K342N, K344R , L345Q, T348I, V369G, T382S, T401I	

Appendix 1: MyTACTIC Biomarker Overview

Specific Tumor Gene Alterations		
Biomarker	**Allowed Alteration Types**	**Arms & excluded indications**
RET	3' RET fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact RET kinase domain	**Arm O:** Pralsetinib • NSCLC, thyroid cancers excluded
ROS1	3' ROS1 fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain	**Arm A**: Entrectinib • NSCLC excluded
ERBB2 (HER2) & MSI-H, dMMR, or TMB ≥10	ERBB2 (HER2) gene amplification or activating mutation as defined above Other ERBB2 (HER2) activating mutations with Medical Monitor approval AND MSI-H, dMMR (as defined below), or TMB ≥10 mut/mb	**Arm J**: Trastuzumab emtansine plus atezolizumab • Breast cancer excluded

Other Genomic Biomarkers		
Biomarker	Alteration Type	Arms & excluded indications
MSI-H	Microsatellite instability high (MSI-H)	**Arm E**: Atezolizumab plus chemotherapy **Arm N:** Atezolizumab plus tiragolumab **Arm J:** Atezolizumab plus Trastuzumab Emtansine • with ERBB2 amplification or mutation • Breast cancer excluded
dMMR	Mismatch repair deficient (dMMR), defined as genetic loss of function of MLH1, MSH2, MSH6 or PMS2	
TMB High	Tumor mutational burden (TMB) ≥10 mutations/megabase as determined by a tissue-based NGS assay	

Appendix 1: MyTACTIC Biomarker Overview

Protein-based Biomarkers		
Biomarker	Alteration Type	Arms & excluded indications
dMMR	Mismatch repair deficient (dMMR), defined as loss of MLH1, MSH2, MSH6 or PMS2 protein	**Arm E**: Atezolizumab plus chemotherapy **Arm N**: Atezolizumab plus tiragolumab **Arm J:** Atezoliumab plus Trastuzumab Emtansine • with ERBB2 amplification or mutation • Breast cancer excluded
PTEN	PTEN Loss by IHC	**Arm D**: Ipatasertib • Triple negative adenocarcinoma of the breast excluded **Arm L**: Ipatasertib plus atezolizumab **Arm M:** Ipatasertib plus paclitaxel • with PIK3CA co-mutation

ALK= anaplastic lymphoma kinase; dMMR= deficient mismatch repair; IHC=immunohistochemistry; HER2= human epidermal growth factor receptor 2; Mb=megabase; MSI-H= microsatellite instability high; mut=mutations; TMB=tumor mutational burden.

Appendix 2
Contraception and Pregnancy Requirements

CONTRACEPTION REQUIREMENTS DURING THE TREATMENT PERIOD FOR WOMEN OF CHILDBEARING POTENTIAL

Female patients of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use effective contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and until the study drug-specific time period listed in Table 1. Women must refrain from donating eggs during this same period.

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

CONTRACEPTION REQUIREMENTS DURING THE TREATMENT PERIOD FOR MEN

Male patients must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

- With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and until the study drug-specific time period listed in Table 1.
- With a pregnant female partner, men must remain abstinent or use a condom during the treatment period until the study drug-specific time period listed in Table 1.

CONTRACEPTIVE METHODS

Abstinence is defined as true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing- intrauterine devices, and copper intrauterine devices. Note that female patients taking pralsetinib must use effective non-hormonal contraceptive methods; hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are

not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Table 1 Contraception Requirements after the Last Dose of Study Drug

	Timeframe after the Last Dose of Study Drug[a]	
Study Drug	Females	Males
Alectinib	90 days	90 days
Atezolizumab	5 months	Not applicable
Capecitabine	6 months	3 months
Docetaxel	6 months	3 months
Entrectinib	5 weeks	90 days
Inavolisib (GDC-0077)	60 days	120 days
Ipatasertib	28 days	28 days
Paclitaxel	6 months	3 months
PH FDC SC	7 months	7 months
Pralsetinib	2 weeks	1 week
Tiragolumab	90 days	90 days
Trastuzumab emtansine	7 months	7 months
Tucatinib	1 week	1 week

[a] If patient is receiving a combination of study drugs, the requirement will last for the time period that is longer.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

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

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 mm but $<$ 15 mm) as well as truly nonmeasurable 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

[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.

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, 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) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and 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.

CLINICAL LESIONS

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

CHEST X-RAY

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

CT 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 intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine 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 nontarget disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

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

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 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 nonmeasurable), 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 nontarget lesions involving the same organ as a single item

on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce 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.

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.

RESPONSE CRITERIA

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 at prior timepoints (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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it 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.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

Table 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.

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.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 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.

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 4
Response Assessment in Neuro-Oncology (RANO) Criteria

RANO CRITERIA FOR HIGH-GRADE GLIOMA

Response	Criteria for High-Grade Glioma
Complete response	Requires **all** of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions • Patients must be off corticosteroids (or on physiological replacement doses only) • Clinical status is stable or improved
Partial response	Requires **all** of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks • No progression of nonmeasurable T1 enhancing disease • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease
Stable disease	Requires **all** of the following: • Patient does not qualify for complete response, partial response, or progression • Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Response	Criteria for High-Grade Glioma (cont.)
Progression	Defined by **any** of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (of no decrease) or best response, on a stable or increasing dose of corticosteroids

Response	Criteria for High-Grade Glioma (cont.)
	• Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of steroids compared with baseline scan or best response after initiation of therapy, not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, seizures, postoperative changes, or other treatment effects) • Presence of any new lesions • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or decreases in corticosteroid dose • Failure to return for evaluation due to death or deteriorating condition • Clear progression of nonmeasurable disease

FLAIR=fluid-attenuated inversion recovery; RANO=Response Assessment in Neuro-Oncology.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

RANO CRITERIA FOR LOW-GRADE GLIOMA

Response	Criteria for Low-Grade Glioma
Complete response	Requires all of the following criteria compared with the baseline scan: • Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely) • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients must be off corticosteroids or only on physiological replacement doses • Patients should be stable or improved clinically
Partial response	Requires all of the following criteria compared with the baseline scan: • ≥50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Minor response	Requires the following criteria compared with baseline: • A decrease of the area of non-enhancing lesion on T2 or FLAIR magnetic resonance imaging between 25% and 50% compared with baseline

Appendix 4: Response Assessment in Neuro-Oncology (RANO) Criteria

Response	Criteria for Low-Grade Glioma
	• No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Stable disease	Is present if the changes do not qualify for complete, partial, or minor response, or progression and requires: • Stable area of non-enhancing abnormalities on T2 or FLAIR imaging • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically

Response	Criteria for Low-Grade Glioma (cont.)
Progression	Defined by <u>any</u> of the following: • Development of new lesions or increase of enhancement (radiological evidence of malignant transformation) • A 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events • Definite clinical deterioration not attributable to other causes apart from the tumor or decrease in corticosteroid dose • Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

FLAIR=fluid-attenuated inversion recovery; RANO=Response Assessment in Neuro-Oncology.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

Appendix 5
Performance Status Scales

ECOG PERFORMANCE STATUS SCALE

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

ECOG=Eastern Cooperative Oncology Group.

Appendix 6
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 7
Moderate and Strong CYP450 Inhibitors, Inducers and Enzyme- and Transporter-Specific Substrates

Examples of strong and moderate CYP3A inhibitors and inducers and combined P-gp and strong CYP3A4 inhibitors are outlined in Table 1.

Examples of cytochrome enzyme-specific substrates are outlined in Table 2

Please note that this is not a comprehensive list of all CYP450 inhibitors, inducers, combined P-gp and strong CYP3A4 inhibitors, and enzyme-/transporter- specific substrates. CYP2C8 inhibitors and inducers include but are not limited to those listed in Table 3. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Table 1 Examples of CYP3A Inhibitors, Inducers, and Combined P-gp and Strong CYP3A4 Inhibitors

CYP3A Inhibitors or Inducers	
Strong Inhibitors	Strong Inducers
Atazanavir, boceprevir, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit, grapefruit juice, idelalisib, indinavir and ritonavir, ketoconazole, nefazodone, ombitasvir and/or dasabuvir, paritaprevir and ritonavir, posaconazole, ribociclib, Seville oranges, starfruit, telithromycin, troleandomycin, voriconazole	Apalutamide, carbamazepine, enzalutamide, mitotane, primidone, phenobarbital, phenytoin, rifampin, St. John's wort
Moderate Inhibitors	Moderate Inducers
Aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Bosentan, efavirenz, etravirine, modafinil
Combined P-gp and Strong CYP3A4 Inhibitors	
Clarithromycin, cobicistat, itraconazole, lopinavir and ritonavir, mifebradil, nelfinavir, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir, ritonavir	

Note: This is not a comprehensive list of all CYP3A inhibitors, inducers, and combined P-gp and strong CYP3A4 inhibitors.

Table 2 Examples of Enzyme-/Transporter-Specific Substrates

Enzyme/Transporter	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP2C8	Repaglinide	
CYP2C9	Celecoxib	Warfarin, phenytoin, tolbutamide
CYP2C19	Omeprazole	
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide
CYP3A4	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, ticagrelor, vardenafil	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
P-gp	Digoxin, dabigatran etexilate, fexofenadine	
BCRP	Rosuvastatin, sulfasalazine, methotrexate, mitoxantrone, topotecan, lapatinib	
OATP1B1/OATP1B3	Asunaprevir, atorvastatin, bosentan, danoprevir, docetaxel, fexofenadine glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid	
OAT1	Adefovir, cefaclor, ceftizoxime, famotidine, furosemide, ganciclovir methotrexate, oseltamivir, carboxylate penicillin G	
MATE1/MATE2-K	Metformin	

Note: This is not a comprehensive list of all enzyme- or transport-specific substrates.

Table 3 CYP2C8 inhibitors/inducers and Their Elimination Half-Lives

Drug[a,b]	Elimination Half-life[c]
Strong Inhibitors	
Gemfibrozil	1–2 hours
Moderate Inhibitors	
Clopidogrel	6 hours
Deferasirox	8-16 hours
Teriflunomide	18-19 days
Moderate Inducer	
Rifampin	3–5 hours

Note: Any additional CYP2C8 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers” (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

b EMA. “Guideline on the investigation of drug interactions” (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug package insert

Appendix 8
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune 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 • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 9
NYHA Functional Classification System for Heart Failure and LVSD NCI CTCAE V5.0 Grading

NYHA Functional Classification System for Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

NYHA=New York Heart Association.

LVSD NCI CTCAE V5 Grading

Investigations					
	Grade				
	1	2	3	4	5
EF decreased [a]	—	Resting EF 50%–40%; 10%–19% drop from baseline	Resting EF 39%–20%; ≥ 20% drop from baseline	Resting EF < 20%	—
Cardiac Disorders					
	Grade				
	1	2	3	4	5
Heart failure [b]	Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities	Symptoms with moderate exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

BNP=B-natriuretic peptide; EF=ejection fraction; IV=intravenous; LVSD=left ventricular systolic dysfunction.

[a] The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.

[b] A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.

https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 10
Arm A: Entrectinib in Patients with ROS1 Fusion-Positive Tumors

11. ARM A: ENTRECTINIB IN PATIENTS WITH ROS1 FUSION-POSITIVE TUMORS

TABLE OF CONTENTS

A.4 MATERIALS AND METHODS

A.4.1 Patients

To be enrolled in Arm A: entrectinib treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

A.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm A: entrectinib treatment:

- ROS1 gene fusion positivity, except patients with non-small cell lung cancer (NSCLC), as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' ROS1 fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Ability to swallow entrectinib intact, without chewing, crushing, or opening the capsules/tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$1% per year during the treatment period and for at least 5 weeks after the last dose of entrectinib; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details on contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$1% per year during the treatment period and for at least 3 months after the last dose of entrectinib, and agreement to refrain from donating sperm during this same period. See Appendix 2 for details on contraception requirements.

A.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm A: entrectinib treatment:

- ROS1 fusion-positive NSCLC
- Prior treatment with crizotinib
- Whole-brain radiotherapy and/or stereotactic radiosurgery for CNS disease within 14 days prior to the start of entrectinib treatment.
- Symptomatic or uncontrolled CNS involvement
  - Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.

  - Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment.
- Requirement for enzyme inducing anti-epileptic drugs (EIAEDs) or use within 14 days or 5 half lives (whichever is longer) prior to the start of entrectinib treatment
  - Use of seizure prophylaxis is allowed as long as patients are taking non-enzyme inducing anti-epileptic drugs (non-EIAEDs).
  - If patients require an anti-epileptic medication, a CYP3A4 non-EIAED can be used such as levetiracetam, valproic acid, gabapentin, topiramate, or lacosamide. Moderate inducers of CYP450, such as dexamethasone or other glucocorticoids, may be used at the discretion of the investigator.
- History of non-pharmacologically induced prolonged corrected QT (QTc) interval (e.g., repeated demonstration of a QTc interval $>$450 ms from ECGs performed at least 24 hours apart)
- History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction $\leq$50% observed during screening for the study
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome)
- Grade $\geq$2 peripheral neuropathy
- Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably affect drug absorption
- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor–induced pneumonitis

  Note: Radiation-induced lung disorders are not included in this exclusion criterion.

A.4.2 Study Treatment

Study treatment in this arm will consist of entrectinib.

A.4.2.1 Formulation and Packaging

Entrectinib will be supplied by the Sponsor as 100-mg and 200-mg capsules.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access. For information on the packaging, handling, and storage, see the Pharmacy Manual and Entrectinib Investigator's Brochure.

A.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 28 day cycles.

Entrectinib will be self-administered by patients orally at home (except on clinic days Section A.6), at the same time each day, on a starting dose of 600 mg/day (three 200-mg capsules per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. Modification may be needed in cases of coadministration with moderate or strong CYP3A4 inducers (See Section A.4.3.2). For more specific dosing instructions, refer to the pharmacy manual.

The capsules should not be opened and the contents of the capsules should not be dissolved. Entrectinib can be taken with or without food. For patients experiencing fatigue, nausea, or other mild tolerability issues, an evening time administration is recommended.

For entrectinib doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken. On Day 1 and on clinic visit days, entrectinib should be taken at the clinic after all the predose assessments have been conducted, at the direction of the study research nurse or treating physician.

A missed dose can be taken within 12 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses)

Guidelines for entrectinib dosage modification and treatment interruption or discontinuation are provided in Section A.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

A.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

A.4.3.1 Permitted Therapy

Seizure prophylaxis with any of the following non-EIAEDs is allowed during the study for patients with controlled asymptomatic CNS involvement: levetiracetam, valproic acid, lacosamide, gabapentin, topiramate, lamotrigine, tiagabine, zonisamide, clonazepam, clobazam, or pregabalin. Note: EIAEDs are not allowed (see Section A.4.3.2).

Moderate inducers of CYP3A, CYP3A4, or CYP3A4/5, such as dexamethasone or other glucocorticoids, may be used at the discretion of the investigator for CNS metastasis. See Appendix 7 for examples of CYP450 inducers, inhibitors, and enzyme-specific substrates.

In certain instances, palliative radiotherapy to specific sites is permitted if considered medically necessary by the investigator. The Sponsor must be notified if palliative radiotherapy is started; however, the need for radiotherapy will generally be considered indicative of progressive disease.

It is recommended to avoid radiotherapy for at least 5 days after the last dose of entrectinib. The irradiated area should be as small as possible and $<25\%$ of the bone marrow reserve.

Entrectinib administration should be withheld during the period of irradiation and for 2 weeks thereafter. If radiation-related toxicities (other than xerostomia) have not normalized to preirradiation levels after 2 weeks of rest, the patient should be discontinued from the study.

Entrectinib treatment has not been specifically observed to interfere with wound healing; therefore, caution is advised on theoretical grounds. Based upon pharmacokinetic considerations, stopping entrectinib treatment is recommended at least 5–7 days prior to major elective surgery and 2–3 days prior to minor surgical procedures. Postoperatively, the decision to reinitiate treatment with entrectinib should be based upon clinical assessment of satisfactory wound healing and recovery from surgery.

No other approved or investigational anti-cancer therapy is permitted during study participation, including chemotherapy, immunotherapy, biological response modifiers, and/or hormonal therapy.

Bone-sparing agents (e.g., bisphosphonates, denosumab) for palliation of bone metastases or for the treatment of osteoporosis or osteopenia are allowed, but initiation of such agents or modification of the pre-study bisphosphonate or denosumab treatment regimen should be done in consultation with the Medical Monitor.

Therapies considered necessary for the patient's well-being (e.g., therapies to manage concomitant chronic pathologies or therapies required for life-threatening medical conditions) may be administered as per the investigator's discretion. For seasonal flu shots, inactivated vaccines are allowed.

Use of concomitant medications that increase or possibly increase the risk of QTc prolongation and/or induce torsades de pointes ventricular arrhythmia must be done with caution or avoided if possible during study participation (see Table 1).

Table 1 Concomitant Medications to Be Used with Caution

Antiarrhythmics	Amiodarone	Procainamide
	Disopyramide	Quinidine
	Dofetilide	Sotalol
	Ibutilide	
Antipsychotics	Chlorpromazine	Quetiapine
	Clozapine	Risperidone
	Haloperidol	Thioridazine
Antibiotics	Azithromycin	Ketoconazole
	Ciprofloxacin	Levofloxacin
	Clarithromycin	Moxifloxacin
	Erythromycin	Ofloxacin
	Fluconazole	Sparfloxacin
	Gatifloxacin	Telithromycin
	Itraconazole	Trimethoprim-sulfa
Antidepressants	Amitriptyline	Imipramine
	Citalopram	Nortriptyline
	Desipramine	Paroxetine
	Doxepin	Sertraline
	Fluoxetine	Venlaxafine
Antiemetics	Ondansetron	Prochlorperazine

A.4.3.2 Prohibited Therapy

The following EIAEDs are prohibited during the study and for at least 14 days or 5 halflives (whichever is longer) prior to initiation of entrectinib: carbamazepine, oxcarbazepine, phenytoin, fosphenytoin-, phenobarbital, and primidone. See Section A.4.3.1 above for alternative anti-epileptic treatment options.

Use of herbal medications (e.g., St. John's Wort) should be avoided when possible.

Entrectinib is mainly eliminated through hepatic clearance and CYP3A4 plays a significant role in the biotransformation of entrectinib. Co-administration of strong or moderate CYP3A4 inhibitors and inducers should be avoided. However, moderate inducers of CYP3A, CYP3A4, or CYP3A4/5, such as dexamethasone or other glucocorticoids, may be used at the discretion of the investigator as clinically indicated per local institutional guidelines. See Appendix 7 or examples of CYP450 inducers, inhibitors, and enzyme-specific substrates.

In vitro, entrectinib exhibited potential to inhibit and induce the activities of CYP3A, and potential for inhibition of CYP2C9 and CYP2D6, which suggests a potential for interaction with other drugs metabolized by these isoforms.

Because of this potential, entrectinib should be avoided or, if necessary, administered with caution with strong CYP3A inhibitors or inducers. Examples of strong and moderate CYP3A inhibitors and inducers are listed in Appendix 7. If coadministration of strong or moderate CYP3A inhibitors with entrectinib is unavoidable, reduce the dose of entrectinib as follows:

- Moderate CYP3A Inhibitors: 200 mg orally once daily
- Strong CYP3A inhibitors: 100 mg orally once daily

A.4.3.3 Prohibited Food

Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit should be avoided during the treatment period.

A.4.4 Entrectinib-Specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the entrectinib treatment arm. Refer to the schedule of activities (Section A.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

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

- Coagulation: INR and aPTT
- Lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

Functional Assessments

- Left-ventricular ejection fraction (LVEF) assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
- Ophthalmological examinations: visual acuity and slit-lamp test
- Single ECG
- Fall risk factor evaluation and monitoring

A.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm A: entrectinib treatment.

A.5.1 Risks Associated with Entrectinib

Entrectinib has been associated with risks such as the following: cognitive disorders (including confusion, mental status changes, memory impairment, and hallucinations), congestive heart failure (CHF), bone fractures, and QT prolongation. Refer to the Entrectinib Investigator's Brochure for a detailed description of anticipated safety risks for entrectinib.

A.5.2 Management of Patients Who Experience Adverse Events with Entrectinib

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

A.5.2.1 Dose Modifications and Interruptions

Adverse events associated with entrectinib can often be managed with concomitant medications, supportive care (see Section A.4.3.1 and Section A.5.2.2), and/or dose modifications as per Table 3.

If an adverse event is considered unrelated to study treatment and results in dose interruption, treatment may resume at the initial dose after the adverse event stabilizes or resolves to Grade 1 or better, as per the investigator's discretion.

If toxicities that are possibly related to entrectinib are not easily managed or corrected, and are not tolerable to the patient, or if there are adverse events that are not acceptable in the investigator's judgment, the patient should have study treatment interrupted until the adverse event resolves to Grade 1 or better. If study treatment is interrupted, dose reduction (if mandated) should occur when study treatment is resumed. All dose reductions should be based on the most severe toxicity observed that is attributable to entrectinib.

If needed, dose reductions may occur in decrements of 200 mg and no more than two dose reductions will be allowed. Accordingly, the possible daily doses of entrectinib are shown in Table 2. For patients on an already reduced dose due concomitant CYP3A4 inducer use, additional dose modification should be done in consultation with Medical Monitor. Dose re-escalation is not permitted for entrectinib.

Table 2 Entrectinib Dose Reductions

Dose Level	Dose (mg QD)
Starting Dose	600
First reduction	400
Second reduction	200

QD = once a day.

Entrectinib treatment may be interrupted for a maximum of 28 days to allow sufficient recovery from any toxicity if a patient is still deriving clinical benefit in the judgment of the investigator.

Table 3 Dose Modifications and Interruptions for Entrectinib-Related Adverse Events

Adverse Drug Reaction	Severity [a]	Dose Modification
Anemia or Neutropenia	Grade 3 or Grade 4	• Withhold entrectinib until recovery to Grade ≤2 or to baseline, then resume treatment at same dose level or reduced dose, as clinically needed.
Cognitive Disorders	Grade ≥ 2	• Withhold entrectinib until recovery to Grade ≤1 or to baseline, then resume treatment at reduced dose. • If event recurs, further reduce dose. • For prolonged, severe, or intolerable events, discontinue as clinically appropriate.
Transaminase Elevations	Grade 3	• Withhold entrectinib until recovery to less than or equal to Grade 1 or to baseline. • Resume at same dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold entrectinib until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	• Permanently discontinue entrectinib.

Table 3 Dose Modifications and Interruptions for Entrectinib-Related Adverse Events (cont)

Adverse Drug Reaction	Severity [a]	Dose Modification
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold entrectinib until improvement of signs or symptoms • Resume entrectinib at same or reduced dose
Congestive Heart Failure	Grade 2 or 3	• Withhold entrectinib until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Grade 4	• Withhold entrectinib until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
QT Interval Prolongation	QTc 481 to 500 ms	• Withhold entrectinib until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold entrectinib until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are not identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue entrectinib
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold entrectinib until adverse reaction resolves or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events

[a] Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

A.5.2.2 Guidelines for Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in the subsections below.

A.5.2.2.1 Nausea and Emesis

For nausea and emesis, treat with standard antiemetics; prophylactic antiemetics are permitted as necessary using institutional guidelines for treatment and/or published guidelines. Refer to Table 1 for concomitant medications that should be administered with caution.

A.5.2.2.2 Diarrhea

Treatment with antidiarrheal drugs may be warranted and should follow institutional and/or published guidelines. If no guidelines exist, then the following recommendations may be instituted:

- For Grade 1 diarrhea, treat with loperamide if needed; no dose modification is necessary.
- For Grade 2 diarrhea, treat with loperamide (4 mg at first onset, then 2 mg every 2–4 hours or after each loose stool, until symptom free for 12 hours). No dose modification is necessary unless the patient is intolerant or symptom is recurrent.
- For Grade $\geq$3 diarrhea (despite use of loperamide), treatment should be withheld until recovery to Grade 1 or better.

A.5.2.2.3 Severe Neutropenia or Anemia

Prophylactic use of granulocyte colony-stimulating factor (G-CSF) or initiation of erythropoietin may be instituted according to the American Society of Clinical Oncology guidelines in patients who are having difficulty with severe neutropenia or anemia. Patients who have been treated for $>$4 weeks with erythropoietin prior to enrolling in the study may continue on the existing treatment.

Patients with neutropenic fever or infection should be hospitalized promptly for intravenous (IV) antibiotic therapy and may receive therapeutic colony stimulating factors as appropriate.

Red blood cell and platelet transfusions should be administered as warranted.

A.5.2.2.4 Pneumonitis or Pneumonia

Investigators must thoroughly evaluate patients who demonstrate potential signs and symptoms of pneumonitis or pneumonia. If a patient has a potential diagnosis of pneumonitis or study drug–related lung injury, the following evaluations and procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) for bacteria, viruses, fungi, protozoa, and mycobacteria
- Blood culture for febrile patients
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum)

- Bronchoscopy with bronchoalveolar lavage (BAL), if appropriate. BAL fluid should be sent for culture and cytology (examined for same pathogens as sputum)
- Lung biopsy (e.g., open or thorascopic preferable; bronchoscopy with transbronchial biopsy), if appropriate
- A plasma sample for B-type natriuretic peptide to evaluate for evidence of congestive heart failure
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of protozoal pneumonia (e.g., Pneumocystis jiroveci)

If clinically appropriate, high-dose corticosteroid treatment should be initiated. Should the event be fatal, an autopsy is highly recommended to confirm or to exclude the diagnosis. For any case of suspected pneumonitis, please contact the Sponsor. See Table 3 for appropriate dose modifications.

A.5.2.2.5 QT Interval Prolongation

In cases of Grade 2 or 3 QT interval prolongation, assess and correct electrolytes and concomitant medications and follow dose modification guidelines in Table 3. In cases of Grade 4 QT interval prolongation, entrectinib should be permanently discontinued.

A.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients in the Entrectinib treatment arm:

- Bone fractures: All grades
- Cognitive disturbances: Grade ≥ 2
- Congestive cardiac failure: Grade ≥ 2
- QT prolongation: Grade ≥ 2
- Syncope: All grades

A.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]	Follow-Up [c]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified		Every 3 Months After Last Dose
(Window)	−28 TO −1 [A]	(±3)	(±3)	≤ 28 days from last study dose	(±14)
Informed consent [d]	x				
Documentation of positive ROS1 gene fusion status by local test [e]	x				
Medical history and baseline conditions [f]	x				
Physical Examination [g]	x	As clinically indicated			
ECOG Performance Status [h]	x	x		x	
Pregnancy test [i]	x	x		x	
Chemistry [j]	x	x		x	
Hematology/CBC with differential [k]	x	x		x	
Coagulation panel [l]	x				
Lipid panel [m]	x				
ECHO/MUGA [n]	x	C3, D1 and as clinically indicated		x [n]	
Single ECG [o]	x	D1 of C1−C3 and every 2 cycles thereafter, and as clinically indicated			
Opthamalogical examinations [p]	x	C2, D1 and as clinically indicated		x	
Fall risk factor evaluation and monitoring [q]	x	x		x	
Response assessment [r, s]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks			

Arm A: Entrectinib In Patients with *ROS1* Fusion-Positive Tumors

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]	Follow-Up [c]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified		Every 3 Months After Last Dose
(Window)	–28 TO –1 [A]	(±3)	(±3)	≤ 28 days from last study dose	(±14)
Pre-treatment tumor tissue sample for central testing (if applicable) [t]		Submit within 21 days of Cycle 1 Day 1			
Whole blood samples [u]	x		see footnote u		
Study drug compliance assessment [v]		x		x	
Study drug dispensing		x			
Adverse events [w]		Collected on an ongoing basis			
Concomitant medications [x]		Collected on an ongoing basis			
Survival follow-up and anticancer therapy [y]					x

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECG=electrocardiogram; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months for up to at least 1 year, until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ROS1 gene fusion status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] Lipids include total cholesterol, triglycerides, LDL, and HDL.

[n] LVEF assessment by ECHO or MUGA to be performed at screening, Cycle 3 Day 1 (±7 days), as clinically indicated, and at the end of treatment (if patient experienced Grade 2 or higher ejection fraction decrease at Cycle 3 or at any time during treatment, or if clinically indicated). The end-of-treatment LVEF is not necessary if the last LVEF assessment was performed within 1 week prior to the end of treatment visit and if the investigator deems it is not clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[o] At study treatment visits (Day 1 of a given cycle), perform pre-dose and 4 hours [± 15 min] post-dose for Cycles 1–3, and pre-dose every 2 cycles thereafter. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[p] Ophthalmologic examinations including at least visual acuity and slit-lamp tests (which may be performed by an optometrist) will be required at Screening, Cycle 2 Day 1, at the end of treatment, and as clinically indicated. Note: The time window for ophthalmologic examinations is ±1 week.

[q] Fall risk evaluation and monitoring: at every visit, patients will be asked about risk factors of fall, weight, nutritional intake, nutritional deficiencies, impaired cognition and health deterioration. Relevant findings will be recorded as adverse events. Additional assessments may be performed at the discretion of the treating physician.

[r] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[s] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[t] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[u] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression for analyses including ctDNA.

[v] Study drug compliance will be reviewed with the patient.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[x] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

[y] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for at least up to 1 year or until death (unless the patient withdraws consent, is lost to follow up or the Sponsor terminates the study), whichever comes first. If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 11
Arm B: Inavolisib (GDC-0077) in Patients with PI3K (PIK3CA) Activating Mutation–Positive Tumors

12. ARM B: INAVOLISIB (GDC-0077) IN PATIENTS WITH PI3K (PIK3CA) ACTIVATING MUTATION–POSITIVE TUMORS

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B.4 MATERIAL AND METHODS

B.4.1 Patients

To be enrolled in Arm B: Inavolisib (GDC-0077) treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to arm-specific criteria below.

B.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm B: Inavolisib (GDC-0077) treatment:

- PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  – H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V

  – Other activating mutations with Medical Monitor approval
- ANC $\geq 1000/\mu L$ within 14 days prior to initiation of study treatment
- Fasting glucose < 126 mg/dL and glycosylated hemoglobin (HbA_{1c}) $< 5.7\%$
- Willingness and ability to swallow inavolisib (GDC-0077) intact, without chewing, or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 60 days after the last dose of inavolisib (GDC-0077); and agreement to refrain from donating eggs during this same period. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential. See Appendix 2 for details regarding contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 120 days after the last dose of inavolisib (GDC-0077), and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

B.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm B: inavolisib (GDC-0077) treatment:

- Primary CNS tumors
- Type 2 diabetes requiring antihyperglycemic medication or any history of type 1 diabetes
- Patients with elevated fasting glucose at baseline (fasting glucose ≥ 126 mg/dL [≥ 7.0 mmol/L]) or HbA1c ≥ 5.7% will be excluded from the study
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Uncontrolled pleural effusion or ascites requiring recurrent drainage procedures twice monthly or more frequently

  Indwelling pleural or abdominal catheters are allowed provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved
- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator and/or study ophthalmologist, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Patients requiring any daily supplemental oxygen
- History of or active inflammatory disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)

  Patients currently receiving immunosuppressants (e.g., sulfasalazines) are considered to have active disease and are, therefore, ineligible.
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
- Clinically significant and active history of liver disease, including severe liver impairment (ChildPugh score B/C), current alcohol abuse, or cirrhosis
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) > 470 ms demonstrated by at least two ECGs > 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval

- Allergy or hypersensitivity to components of the GDC-0077 formulation
- Any symptomatic active lung disease, including pneumonitis

B.4.2 Study Treatment

Study treatment in this arm will consist of inavolisib (GDC-0077).

B.4.2.1 Formulation and Packaging

Inavolisib (GDC-0077) will be supplied by the Sponsor as an immediate-release tablet formulation (3-mg and 9-mg).

The 3-mg and 9-mg tablets should be stored at or below 86°F (30°C) and protected from light. Patients should be cautioned to keep the tablets in the foil-protected cards supplied, and to NOT remove them except immediately prior to consumption.

For information on the packaging, handling and storage, see the Pharmacy Manual and Inavolisib (GDC-0077) Investigator's Brochure.

B.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 28-day cycles.

Inavolisib (GDC-0077) will be self-administered by patients orally at home (except on clinic days) at the same time each day, on a starting dose of 9 mg/day (one 9-mg tablet per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The tablets will be swallowed whole (not chewed) with 8 ounces (240 mL) of fluid, preferably water.

For inavolisib (GDC-0077) doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator’s discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 9 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for inavolisib (GDC-0077) dosage modification and treatment interruption or discontinuation are provided in Section B.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

B.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

B.4.3.1 Permitted Therapy

Patients who experience toxicities should be treated symptomatically as clinically indicated.

Patients treated with antiseizure medications or warfarin should have levels monitored regularly.

Patients who use oral contraceptives or other allowed maintenance therapy as specified in the eligibility criteria (see Section B.4.1.1 and Appendix 2) should continue their use.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug.

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.

Multivitamins, calcium, and vitamins C, D, and E supplements are allowed. However, due to the potential for drug-supplement interactions, and variability among suppliers and batches, the use of other dietary supplements is cautioned.

B.4.3.2 Prohibited Foods and Therapies

Use of the following foods and therapies is prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified below:

- Any concomitant therapy intended for the treatment of cancer, whether approved by the U.S. Food and Drug Administration (FDA) or experimental, including chemotherapy, radiotherapy, immunotherapy, biologic therapy, herbal therapy, or hormonal therapy, except for those administered as study treatment.

- Primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor [G-CSF], and granulocyte-macrophage colony-stimulating factor [GM-CSF]) is not permitted, however, they may be used to treat treatment-emergent neutropenia or anemia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines or as secondary prophylaxis if dose reduction or delay is not considered a reasonable alternative after discussion with the Sponsor.

Patients who require the use of any prohibited therapies will be discontinued from study treatment and followed for safety outcomes for 28 days after their last dose of inavolisib (GDC-0077), or until they receive another anticancer therapy, whichever occurs first.

In vitro data suggest that inavolisib (GDC-0077) is metabolized by cytochrome P450 3A4 (CYP3A4) and that there is a low to moderate potential for a drug-drug interation (DDI) with any medication that strongly inhibits or induces this enzyme. Therefore, strong/moderate CYP3A4 inhibitors and inducers should be avoided (see Appendix 7). If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to its concomitant administration with inavolisib (GDC-0077).

In vitro data also suggest that inavolisib (GDC-0077) is a substrate of the efflux transporter P-glycoprotein (P-gp) and concomitant use of inhibitors of P-gp is not recommended in this study.

- Inhibitors of P-gp include, but not limited to: ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar, valspodar, grapefruit juice, grapefruit supplements, and Seville oranges

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication strongly inhibits or induces CYP3A4, or inhibits P-gp. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

B.4.4 Arm-Specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the inavolisib (GDC-0077) treatment arm. Refer to the schedule of activities (Section B.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation panel: INR and aPTT
- Fasting blood glucose, HbA_{1c}
- Amylase, lipase
- Fasting lipid panel: total cholesterol, triglycerides, LDL, and HDL

Functional Assessments

- Ophthalmologic examination (slit-lamp tests and visual acuity)
- 12 lead electrocardiogram (ECG)

B.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm B: inavolisib (GDC-007) treatment.

B.5.1 Risks Associated with Inavolisib (GDC-0077)

Inavolisib (GDC-0077) has been associated with risks such as the following: hyperglycemia, stomatitis/mucositis, gastrointestinal inflammation, rash, lung inflammation/pneumonitis, immunosuppression with increased risk of infection, potential permanent reproductive sterility, ocular toxicity, and potential drug-drug interaction with CYP3A4, as their concentration may be decreased with concomitant administration. Refer to the Inavolisib (GDC-0077) Investigator's Brochure for a detailed description of anticipated safety risks for inavolisib (GDC-0077).

B.5.2 Management of Patients Who Experience Adverse Events with Inavolisib (GDC-0077)

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases. In general, for the management of specific adverse events of Grade ≥ 3 outlined below, inavolisib (GDC-0077) administration should be interrupted.

B.5.2.1 Dose Modifications and Interruptions

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

Patients may hold the inavolisib (GDC-0077) for up to 28 consecutive days in order to recover from toxicity or an adverse event related to the study drug.

If needed, dose reductions may occur in decrements of 3 mg and no more than two dose reductions will be allowed. Accordingly, the possible daily doses of inavolisib (GDC-0077) are shown in Table 1.

If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued. Dose re-escalation is not permitted for inavolisib (GDC-0077).

Table 1 Inavolisib (GDC-0077) Dose Reductions

Dose Level	Inavolisib (GDC-0077)
Starting dose	9 mg QD
First dose reduction	6 mg QD
Second dose reduction	3 mg QD
Third dose reduction	Not permitted

QD = once a day.

Inavolisib (GDC-0077) treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If inavolisib (GDC-0077) has been withheld for > 28 consecutive days because of treatment-related toxicity, the patient should be discontinued from inavolisib (GDC-0077). Inavolisib (GDC-0077) may be suspended for reasons other than toxicity (eg, surgical procedures), however inavolisib (GDC-0077) should be interrupted at least 48 hours in advance of surgery and resumed only upon resolution to baseline of any sequelae of the procedure, including adequate wound healing. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of > 28 consecutive days, study drug may be restarted upon consultation with the Medical Monitor.

B.5.2.2 Guidelines for Management of Specific Adverse Events

Guidelines for management of specific adverse events are provided in the subsections below.

B.5.2.2.1 Hyperglycemia

Guidelines for management of hyperglycemia are summarized in Table 2.

Table 2 Management of Hyperglycemia

Fasting Glucose Value	Action to be Taken
> ULN to 160 mg/dL (8.9 mmol/L)	• Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist • Provide home glucose monitoring to high risk patients and educate to check fasting glucose at home [a] • Consider oral anti-diabetic medications (e.g., metformin) for high risk patients [a] • Recheck in 3 days and adjust medications as needed [b] • Continue current dose level of inavolisib (GDC-0077)
> 160 to 250 mg/dL (> 8.9–13.9 mmol/L)	• Interrupt inavolisib (GDC-0077) dose until hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L [f] • Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor) [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed [b] • Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist • Initiate fasting home glucose monitoring • Resume current dose level of inavolisib (GDC-0077) when hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L • If fasting blood glucose persists > 200–250 mg/dL or > 13.9–27.8 mmol/L for 7 days despite above interventions, discuss with Medical Monitor [f]
> 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Interrupt inavolisib (GDC-0077) • Manage hyperglycemia as per standard of care [c,d] • Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor) [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed [b] • Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist • Initiate fasting home glucose monitoring • If hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L within 7 days, may resume at current dose level of inavolisib (GDC-0077) • If hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L in ≥ 8 days, reduce inavolisib (GDC-0077) dose by one dose level when treatment resumes [e] • If hyperglycemia > 250–500 mg/dL or > 13.9–27.8 mmol/L recurs within 30 days, reduce inavolisib (GDC-0077) dose by one dose level [e]

Table 2 Management of Hyperglycemia (cont.)

Fasting Glucose Values	Action to be Taken
> 500 mg/dL (> 27.8 mmol/L)	• Interrupt inavolisib (GDC-0077) • Manage hyperglycemia as per standard of care [c,d] • Assess for volume depletion and ketosis and administer appropriate intravenous or oral hydration • Start or increase the dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor) [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed [b] • Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist • Initiate fasting home glucose monitoring • When hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L, reduce inavolisib (GDC-0077) dose by one dose level when treatment resumes [e] • If hyperglycemia > 500 mg/dL or > 27.8 mmol/L recurs within 30 days, permanently discontinue inavolisib (GDC-0077)

BMI = body mass index; SGLT2 = sodium-glucose transport protein 2; ULN = upper limit of normal.

[a] High-risk factors for diabetes include pre-diabetes, overweight, obese, BMI ≥ 30 kg/m^2, hemoglobin A_{1C} ≥ 5.7%, over 45 years of age, family history of diabetes, certain ethnicities, inactive lifestyle, and history of gestational diabetes

[b] Fasting glucose should be checked by finger stick or lab value (if patient has scheduled appointment) **PRIOR** to dosing. Oral anti-diabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤ 160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to a maximum dose allowed as per local prescribing information, given in divided doses, as tolerated. Please see local prescribing information of individual oral anti-diabetic agent for dosing guidelines

[c] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib (GDC-0077) exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short term insulin is allowed to control blood glucose levels, but goal should be to maintain on oral agents once acute episode resolves.

[d] It is recommended that the patient is re-assessed within 24 hours and preferably the same day for assessments of hydration status and renal function.

[e] A maximum of two dose reductions will be allowed.

[f] If, in the investigator's opinion, the benefit-risk assessment favors continued inavolisib (GDC-0077) dosing without interruption, inavolisib (GDC-0077) may be continued without interruption upon discussion with Medical Monitor once patients are managed on anti-diabetic agent(s) and fasting glucose ≤ 200 mg/dL or ≤ 11.1 mmol/L. It is recommended that patients be instructed to utilize a glucometer to monitor fasting glucose and to call the clinic if fasting glucose > 200 mg/dL or > 11.1 mmol/L prior to inavolisib (GDC-0077) dosing at home

The anti-hyperglycemic agent metformin should be used first-line for the management of sustained Grade 2 and Grade 3 hyperglycemia. Investigators should exercise caution in the dosing and management of patients receiving metformin in combination with inavolisib (GDC-0077) and must be vigilant for signs of renal impairment and metformin toxicity. In the event metformin is not tolerated or not sufficient, another anti-hyperglycemic medication(s) may be added to or used in place of metformin. Preferred agents include sodium-glucose transport protein 2 (SGLT2) inhibitors, pioglitazone, and dipeptidyl peptidase 4 (DPP4) inhibitors, where available and considered appropriate by investigators.

Patients at risk for developing hyperglycemia, such as obese and pre-diabetic patients, may initiate treatment with metformin on Day 1 of the study at the treating investigator's discretion.

B.5.2.2.2 Diarrhea

Guidelines for management of diarrhea are summarized in Table 3.

Table 3 Management of Diarrhea

Diarrhea	Action to Be Taken
Grade 1	• Adequate treatment with anti-diarrheals [a] and maximum supportive care [b]
Grade 2	• Adequate treatment with anti-diarrheals and maximum supportive care • Close monitoring • Interrupt inavolisib (GDC-0077) until recovery to Grade ≤ 1, then may resume at the same dose • If recurs within 30 days, reduce inavolisib (GDC-0077) by one dose level
Grade 3	• Interrupt inavolisib (GDC-0077) until recovery to Grade ≤ 1, then reduce by one dose level. Manage as per Grade 2 diarrhea guidelines. • If recurs within 30 days after initiation of the first dose reduction, reduce inavolisib (GDC-0077) by one dose level. If recurs within 30 days from the second dose reduction, permanently discontinue inavolisib (GDC-0077).
Grade 4	• Permanently discontinue inavolisib (GDC-0077)

[a] Initiate loperamide (Imodium®) dose with 4 mg, then 2 mg every loose stool up to 16 mg/day. May consider using combination of loperamide and Lomotil® (diphenoxylate and atropine). May initiate second-line therapy (e.g., octreotide) if Grade ≥ 2 diarrhea persists after 48 hours of treatment with loperamide and/or Lomotil®.

[b] Supportive care: initiate appropriate dietary modification, hydration therapy and electrolyte supplements when clinically indicated. Dietary modification: stop all lactose-containing products and eat small meals; encourage adequate hydration with salt-containing liquids such as broth or Gatorade®.

B.5.2.2.3 Inflammatory Colitis

Guidelines for management of diarrhea are summarized in Table 4.

Table 4 Management of Inflammatory Colitis

Colitis	Action to Be Taken
Grade 1	• Close monitoring and treat as appropriate
Grade 2	• If colitis-related symptoms do not improve to Grade ≤ 1 after 48 hours of anti-diarrheals, start treatment with oral corticosteroid [a] • Interrupt inavolisib (GDC-0077) until recovery to Grade ≤ 1, then may resume at the same dose or one dose level lower per investigator evaluation • If recurs within 30 days, reduce inavolisib (GDC-0077) by one dose level
Grade ≥ 3	• Treat with high dose corticosteroids (IV solumedrol or PO prednisone) [b] • Consider colonoscopy • Interrupt inavolisib (GDC-0077) until recovery to Grade ≤ 1, then reduce by one dose level • If Grade 3 recurs, permanently discontin inavolisib (GDC-0077) • If Grade 4, permanently discontinue inavolisib (GDC-0077)

IV = intravenous; PO = by mouth; QD = once daily.

[a] 20–40 mg prednisone PO QD (starting dose).

[b] For severe grades, may also consider IV solumedrol 16 – 20 mg every 8 hours, or prednisone 60 – 80 mg PO QD equivalent to start.

B.5.2.2.4 Stomatitis/Oral Mucositis

Guidelines for management of stomatitis/oral mucositis are summarized in Table 5.

For any grade stomatitis/mucosal inflammation, aggressive mouth care that includes mouthwash formulations (e.g., combinations of corticosteroid, local anesthetic, antihistamine, antacid, antifungal and/or antibiotics) may be implemented to help manage symptoms. Diet should be modified (e.g., avoidance of spicy foods) and harsh mouth washes (e.g., Listerine®) should be avoided.

A compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment, and/or used reactively with the first appearance of symptoms. No food or drink should be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05–0.5%, fluocinolone acetonide 0.025–0.05%, clobetasol propionate 0.025%) may be implemented. Patients should avoid alcohol-,

hydrogen peroxide-, iodine-, or thyme-containing products as they may exacerbate the condition. Died should be modified (e.g., avoidance of spicy foods), and harsh mouth washes (e.g., Listerine®) should be avoided.

Table 5 Management of Stomatitis/Oral Mucositis

Stomatitis/ Mucosal Inflammation	Action to Be Taken
Grade 1	• Monitor symptoms and initiate management (see above). Re-evaluate within 48 – 72 hours
Grade 2	• Interrupt inavolisib (GDC-0077) and manage until Grade ≤ 1 • When stomatitis/oral mucositis improves to Grade ≤ 1, resume dosing at the same dose • For recurrent Grade 2 stomatitis or oral mucositis within 30 days, resume dosing at one dose level lower
Grade ≥ 3	• Interrupt inavolisib (GDC-0077) and manage until Grade ≤ 1 • When stomatitis/oral mucositis improves to Grade ≤ 1, resume dosing at one dose level lower • If Grade 4, permanently discontinue inavolisib (GDC-0077)

B.5.2.2.5 Rash

Guidelines for management of rash are summarized in Table 6.

Table 6 Management of Rash

Rash	Action to Be Taken
Grade 1	• Continue inavolisib (GDC-0077) dosing and monitor for changes in severity • Consider prescribing topical corticosteroids [a] and/or antihistamines
Grade 2	• Interrupt inavolisib (GDC-0077) treatment • Treat rash per standard of care, including topical and/or oral corticosteroids, [b] and/or antihistamines • When rash resolves to Grade ≤1, resume inavolisib (GDC-0077) at the same dose or one dose level lower per investigator evaluation • If Grade 2 rash recurs within 30 days, reduce inavolisib (GDC-0077) by one dose level when treatment resumes
Grade ≥3	• Interrupt inavolisib (GDC-0077) treatment • Treat rash with topical and/or systemic corticosteroids (oral or IV) and antihistamines • If rash resolves to Grade ≤1 within 28 days of interruption, reduce inavolisib (GDC-0077) by one dose level when treatment resumes • If rash does not resolve to Grade ≤1 within 28 days or interruption, discontinue inavolisib (GDC-0077) • Consider dermatologist consultation and skin biopsy

IV = intravenous.

[a] Suggested topical steroids include hydrocortisone 2.5% to face 2× daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body 2× daily.

[b] Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by taper (e.g., 60 mg × 2 days, 40 mg×2 days, 20 mg×2 days, etc.).

Patients with severe rash should also be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. Permanently discontinue patients for any rash with concurrent signs/symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic/anaphylactoid reaction or with painful desquamation or mucosal involvement suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis or with other life-threatening complications. Dermatological consultation is recommended.

B.5.2.2.6 Pneumonitis

Guidelines for management of pneumonitis are summarized in Table 7.

Table 7 Management of Pneumonitis

Grade	Intervention	Investigation	Inavolisib (GDC-0077) Dose Modification and Management
Grade 1	No specific therapy required	Chest CT scan. Repeat CT at least every 8 weeks until return to baseline. Consider pulmonologist/ respirologist consult. Advise patient to promptly report new or worsening respiratory symptoms.	No action
Grade 2	Prescribe corticosteroids if cough is troublesome and infectious etiology is ruled out. Taper as clinically indicated	Chest CT scan. Repeat CT at least every 8 weeks until return to baseline. Consider PFTs. Obtain pulmonologist/ respirologist consult.	Hold inavolisib (GDC-0077) as long as corticosteroids are being given. When pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroid treatment, resume inavolisib (GDC-0077) dosing at the same inavolisib (GDC-0077) dose or one dose level lower per investigator evaluation. For recurrent Grade 2 event, resume inavolisib (GDC-0077) dosing at one dose level lower.
Grade 3	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated	Chest CT scan. Repeat CT at least every 8 weeks until return to baseline. Consider PFTs and bronchoscopy. Obtain pulmonologist/ respirologist consult.	Hold inavolisib (GDC-0077) as long as corticosteroids are being given. When pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroids, resume inavolisib (GDC-0077) dosing at one dose level lower.
Grade 4	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated	Chest CT scan. Repeat CT at least every 8 weeks until return to baseline. Consider PFTs. Obtain pulmonologist/ respirologist consult. Bronchoscopy is recommended.	Permanently discontinue inavolisib (GDC-0077).

CT = computed tomography (scan); PFT = pulmonary function tests.

B.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients receiving inavolisib (GDC-0077):

- Grade ≥3 hyperglycemia
- Grade ≥3 stomatitis or mucosal inflammation
- Grade ≥3 rash
- Grade ≥3 diarrhea
- Grade ≥2 pneumonitis
- Grade ≥2 colitis or enterocolitis
- Grade ≥3 ALT or AST elevation

B.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive PIK3CA activating mutation status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
Coagulation panel [l]	x	x		x
Fasting lipid panel, amylase, lipase [m]	x	x		x
Fasting HbA_{1C} [n]	x			
Fasting blood glucose [o]	x	x	see footnote o	
Ophthalmologic examination [p]	x	C6, D1 and as clinically indicated		x
12-lead ECG [y]	x	As clinically indicated		
Response assessment [q, r]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [s]		Submit within 21 days of C1, D1		
Whole blood samples [t]	x		see footnote t	

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Study drug compliance assessment [u]		x		x
Study drug dispensing		x		
Post-treatment hyperglycemia follow-up [v]		As clinically indicated		
Adverse events [w]	x [q]	Collected on an ongoing basis		*x* [w]
Concomitant medications [x]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; MRI=magnetic resonance imaging; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1, with the exception of glucose. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive PIK3CA activating mutation status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. With the exception of fasting blood glucose, results that are obtained within 7 days of Cycle 1, Day 1 do not have to be repeated on Cycle 1 Day 1; fasting blood glucose must be assessed within 24 hours of Cycle 1, Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] Fasting lipid panel (total cholesterol, triglycerides, LDL, HDL) and amylase and lipase. Patients must have been fasting 8 hours prior to blood draw. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[n] Repeat HbA1c should be performed after 3 months if the last value was more than 7.5% or as clinically indicated.

[o] Fasting (≥ 8-hour fast) glucose sample. For the first cycle, glucose should be measured in-clinic on C1D1 and daily by home glucometer after overnight fasting, with weekly phone visits with site staff to review results and assess any potential signs or symptoms of hyperglycemia. For Cycle 2, fasting glucose should be measured twice weekly at home. Patients should notify their physician if any abnormal values are measured. Additionally, fasting plasma glucose should be checked in-clinic (or at an offsite lab if in-clinic is not feasible) for Day 1 of each subsequent cycle, as well as Day 15 of cycles 1 and 2 and recorded in the CRF. If an offsite lab is used to assess glucose, a phone visit should be conducted to review results and assess any potential signs or symptoms of hyperglycemia. For Cycle 1 and Cycle 2, samples should be drawn within 24 hours; for all other subsequent cycles, samples should be drawn within 48 hours prior to study drug administration at the clinic; glucose results must be available and reviewed prior to dosing. In addition, patients may be instructed to monitor fasting glucose more frequently via use of home glucometer.

[p] Ophthalmologic examinations including at least visual acuity and slit-lamp tests (which may be performed by an optometrist) will be required at screening, at Cycle 6, at the end of treatment, and as clinically indicated. Note: The time window for ophthalmologic examinations is ±1 week.

[q] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[r] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[s] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[t] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[u] Study drug compliance will be reviewed with the patient.

[v] Patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment and those patients with events of hyperglycemia ongoing at the end of the 28-day safety follow-up, will undergo additional safety follow-up assessments monthly until resolution of their fasting glucose to baseline levels, complete down-titration of their anti-hyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the patient initiates another anti-cancer therapy.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[x] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

[y] A single 12-lead ECG should be performed as specified, and additionally if clinically indicated during the study treatment period. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

B.7 REFERENCES

Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18:654–62

Appendix 12
Arm C: Alectinib in Patients with ALK Gene Fusion-Positive Tumors

13. ARM C: ALECTINIB IN PATIENTS WITH ALK GENE FUSION-POSITIVE TUMORS

TABLE OF CONTENTS

C.4 MATERIALS AND METHODS

C.4.1 Patients

To be enrolled in Arm C: alectinib treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

C.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm C: alectinib treatment:

- ALK gene fusion positivity, in indications other than NSCLC, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' ALK fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq 1000/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of alectinib; and agreement to refrain from donating eggs during this same period. See Appendix 2 for detailed contraception requirements.
- For males with female partners of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of alectinib, and agreement to refrain from donating sperm during this same period. See Appendix 2 for detailed contraception requirements.

C.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm C: alectinib treatment:

- ALK-positive non-small cell lung cancer (NSCLC)
- Inability to swallow pills
- Any gastrointestinal disorder that may affect absorption of oral medications, such as refractory vomiting, malabsorption syndrome, external biliary shunt, or significant bowel resection that would preclude absorption of alectinib
- Detection of the following ALK point mutations: I1171N/S, G1202R
- Symptomatic or uncontrolled CNS involvement

  - Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.
  - Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of alectinib treatment.
- Liver disease, characterized by any of the following:
  - Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices
  - Active autoimmune, alcoholic, or other types of acute hepatitis
- History of organ transplant
- Symptomatic bradycardia
- History of hypersensitivity to any of the additives in the alectinib drug formulation

  This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.

C.4.2 Study Treatment

Study treatment in this arm will consist of alectinib.

C.4.2.1 Formulation and Packaging

Alectinib will be supplied by the Sponsor as 150-mg capsule. Each capsule contains 150 mg of alectinib hydrochloride (as free base), lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate (SLS), magnesium stearate and carboxymethylcellulose calcium, encapsulated in a capsule shell consisting of hypromellose, carrageenan, potassium chloride, titanium dioxide, and carnauba wax.

The formulation contains SLS as a surfactant excipient. This excipient is known to be associated potentially with gastrointestinal (GI) adverse events such as nausea, vomiting, diarrhea, and abdominal pain.

For information on the packaging, handling and storage, see the Pharmacy Manual and Alectinib Investigator's Brochure.

C.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 28 day cycles.

Alectinib will be self-administered by patients orally at home (except on clinic days), at the same times each day, on a starting dose of 600 mg (four 150-mg capsules) twice a day (BID) until disease progression, intolerable toxicity, or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The capsules should not be opened and the contents of the capsules should not be dissolved. Alectinib should be taken with food.

For alectinib doses to be administered at home, a sufficient number of capsules should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 6 hours of the scheduled time. If the missed dose time is greater than 6 hours, or if the patient vomits the dose, the patient should wait until the next scheduled time and take the next scheduled dose. Patients should not take two doses at the same time to make up for a missed dose.

Guidelines for alectinib dosage modification and treatment interruption or discontinuation are provided in Section C.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

C.4.3 Concomitant Therapy

C.4.3.1 Permitted Therapy

The medications and/or treatments below are permitted:

- Local therapy (e.g., stereotactic radiotherapy or surgery) may be given in patients with isolated asymptomatic CNS progression (e.g., new CNS oligometastases) after discussion with the Sponsor.

Caution should be exercised when the following medications are co-administered with alectinib:

- For medications that are substrates of P-gp transporter or breast cancer resistance protein transporter, the investigator should carefully assess the risks against the benefits when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration

cannot be avoided, it is recommended that drug levels and/or signs for toxicity are carefully monitored.

C.4.3.2 Prohibited Therapy

Use of the following therapies (e.g. prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) is prohibited during the study and for at least 14 days prior to initiation of alectinib treatment, unless otherwise specified below. Exceptions to restrictions of the concomitant therapies listed below may be made if the rationale is discussed and documented between the investigator and the Sponsor's Clinical Pharmacologist.

- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins while on study treatment

  Note: The use of systemic corticosteroids for the management of CNS metastases may be permitted upon discussion with the Sponsor.
- Systemic chemotherapy
- Radiotherapy/radionuclide therapy except for palliative radiotherapy to bone lesions or for pain control

  If palliative radiation is indicated, palliative radiation may start within 24 hours of the last dose of alectinib, unless, in the judgment of the investigator, patient safety will require a longer washout period prior to palliative therapy. Dosing of alectinib may resume with the resolution of any radiation toxicity to Grade 1 or better.
- Additional investigational drug (except during the follow-up period)

The list of medications provided above is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet reference provided below when determining whether a certain medication may interact with alectinib. In addition, the investigator should contact the Sponsor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

C.4.4 Arm-specific Assessments

Arm-specific assessments for patients receiving alectinib are displayed in the Schedule of Activities (see Section C.6).

Local Laboratory Assessments

- Chemistry: blood creatine phosphokinase (CPK)
- Liver Function: ALT, AST, total bilirubin, direct bilirubin

Vital Signs

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

Electrocardiograms (ECGs)

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedules of activities (see Section C.6), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine or semi-supine position for at least 5 minutes. The same recording position (supine or semi-supine) should be used for each patient throughout the study. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site. In the event that the ECG machine does not directly provide results for RR and/or QTcF, these parameters can be derived using the following formulae:

QTcF—Fridericia's correction for QTc measurement (if not provided directly by the ECG machine):

$$QTcF\ (ms) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$$

RR Interval Formula (if not provided directly by the ECG machine):

RR (ms) = 60000/heart rate (bpm)

Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. Standard-of-care treatment may be instituted per the discretion of the investigator. The

investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

C.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm C: alectinib treatment.

C.5.1 Risks Associated with Alectinib

Alectinib has been associated with risks such as the following: interstitial lung disease including pneumonitis, hepatotoxicity, anemia including hemolytic anemia, gastrointestinal disorders (nausea, vomiting, constipation, diarrhea, stomatitis), photosensitivity, skin rash, vision disorders (including blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia and diplopia), edema, bradycardia, abnormal renal function (elevated serum creatinine, acute kidney injury), severe myalgia and blood CPK increase, dysgeusia, increased alkaline phosphatase, and weight increase. Refer to the Alectinib Investigator's Brochure for a detailed description of anticipated safety risks for alectinib.

C.5.2 Management of Patients Who Experience Adverse Events with Alectinib

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

C.5.2.1 Dose Modifications and Interruptions

The dose of alectinib can be reduced in steps of 150 mg up to 2 times for management of drug-related toxicities (i.e., from 600 mg BID to 450 mg BID and then from 450 mg BID to 300 mg BID) (see Table 1). Dose re-escalation is not permitted for alectinib.

Table 1 Alectinib Dose Reductions

Dose Reduction Schedule	Dose Level
Starting dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

If further dose reduction is indicated after two dose-reductions, the patient must discontinue alectinib. Administration of a dose below 300 mg BID is not allowed.

If alectinib has been withheld for >21 days because of toxicity, the patient should be discontinued from alectinib. Alectinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) in consultation with the Medical Monitor. The investigator and the Sponsor will determine the acceptable length of treatment interruption.

C.5.2.2 Guidelines for Management of Specific Adverse Events

Guidelines for management of specific adverse events are provided in the subsections below (Table 2).

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities Associated with Alectinib

Event	Action to Be Taken
All AEs **related** [a] to alectinib (unless otherwise specified in this table) + Hepatotoxicity AEs (irrespective of relatedness)	• Grade 4: Temporarily interrupt alectinib for a maximum of 21 days after which the drug must be permanently withdrawn. If improvement to Grade ≤1 or baseline does not occur within 3 weeks, permanently discontinue alectinib. First episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. Second episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID. Third episode: Permanently discontinue alectinib. Please note that dose should not be reduced below 300 mg BID. • Grade 3: Temporarily interrupt alectinib for a maximum of 21 days after which drug must be permanently withdrawn. First episode: If improvement to Grade ≤ 1 or baseline occurs within 10 days, alectinib may be restarted at the original dose or dose reduced by 150 mg (1 capsule) as per investigator discretion. If improvement to Grade ≤1 or baseline occurs after 10 days but within 21 days, then alectinib dose must be decreased by 150 mg (1 capsule BID). Second episode: If improvement to Grade ≤1 or baseline occurs within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. Third episode: Permanently discontinue alectinib. • Grade 2: To be managed at the investigator's discretion. Please note that alectinib cannot be interrupted for more than 21 days and cannot be dose reduced below 300 mg BID. • Grade **1**: No action required
Interstitial lung disease/pneumonitis	Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis. **Regardless of relatedness to alectinib**, study drug should be permanently discontinued in patients diagnosed with interstitial lung disease/pneumonitis of any grade.
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.5 and Section 5.3.5.7 At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible.

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities Associated with Alectinib (cont.)

Event	Action to Be Taken
Hepatotoxicity (cont.)	Regardless of relatedness to alectinib, the grade-dependent rules for dose interruptions and dose modification outlined in the first section of this table must be followed. **In addition**, study drug treatment has to be permanently discontinued if any of the following occurs: • First observation of ALT or AST $>8\times$ ULN • ALT or AST $>5\times$ ULN for more than 2 weeks • First observation of ALT or AST $>3\times$ ULN and total bilirubin $>2\times$ ULN • First observation of ALT or AST $>3\times$ ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [$>5\%$]). • Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pretreatment levels and/or an adequate explanation of the abnormal value is found. • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria.
Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea, stomatitis)	The events are expected to be minimized by taking the study drug with a meal. If GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sunscreen and lip balm of at least SPF 50 to help protect against potential sunburn during this period. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.
Vision disorders	Investigators should consider referring the patients for an ophthalmologic evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity and to advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities Associated with Alectinib (cont.)

Event	Action to Be Taken
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.
Abnormal renal function AEs	Kidney function laboratory abnormalities are to be reported as AEs if they fulfil the criteria listed in Section 5.3.5.5. If at any time during the study treatment serum creatinine increases by ≥2× over the baseline visit value, the patient has to be carefully monitored. All underlying factors that may have acutely impacted serum creatinine levels need to be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate, etc.). Any serum creatinine value that is increased by ≥2× over the baseline-visit value requires repeat testing. • For Grade 1 and Grade 2 AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlines in the first section of this table. • For Grade 3 AEs related to alectinib, temporarily interrupt alectinib until serum creatinine recovers to Grade 1 or baseline, then resume at reduced dose. • For Grade 4 AEs related to alectinib, permanently discontinue study drug.
Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs if they fulfil the criteria listed in Section 5.3.5.5. Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be monitored in patients reporting these symptoms. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Bradycardia [b]	**Grade 2 or Grade 3** (symptomatic; may be severe and medically significant, medical intervention indicated) • Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia, or to a heart rate of ≥ 60 bpm. • If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose (refer to Section C.5.2.1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. **Grade 4** (life-threatening consequences; urgent intervention indicated) • Permanently discontinue if no contributing concomitant medicinal product is identified. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose (refer to Section C.5.2.1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated. • Permanently discontinue in case of recurrence.
Hemolytic anemia	• **If hemoglobin concentration is <10 g/dl (Grade ≥2) and hemolytic anemia is suspected**, withhold alectinib and initiate appropriate laboratory testing, in accordance with local clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (refer to Section C.5.2.1 upon resolution, with improvement of hemoglobin to Grade ≤ 1 or baseline, or permanently discontinue alectinib. • In case of anemia of non-hemolytic mechanism assessed as related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.

AE = adverse event; BID = twice a day; CPK = creatine phosphokinase; GI = gastrointestinal; ULN = upper limit of normal.

Note: Diarrhea, nausea, and vomiting should be handled with best supportive care first before considering dose modification. Preexisting pleural effusion will not be considered as an adverse event.

[a] Please refer to Section 5.3.4 to determine whether event should be assessed as related or unrelated.

[b] Heart rate less than 60 bpm.

C.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

There are no additional adverse events of special interest for Arm C other than those specified in Section 5.2.3.

C.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
Day (Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [c]	x			
Documentation of positive ALK gene fusion status by local test [d]	x			
Medical history and baseline conditions [e]	x			
Physical Examination [f]	x	As clinically indicated		
Vital Signs [g]	x	x		
ECOG Performance Status[h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x	D15 of first 3 cycles [k]	x
Hematology/CBC with differential [l]	x	x		x
CPK	x	C1, D1 and as clinically indicated	C1, D15	
12-lead ECG [m]	x	As clinically indicated		
Response assessments [o, p]	x	Every 8 (± 1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [q]		Submit within 21 days of C1, D1		
Whole blood samples [r]	x		See footnote s	
Study drug compliance assessment [n]		x		x
Study drug dispensing		x		
Adverse events [s]	x	Collected on an ongoing basis		*x* [s]
Concomitant Medications [t]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CPK=creatine phosphokinase; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] Informed consent must be documented before any study-specific screening procedure is performed.

[d] Confirmation positive ALK gene fusion status should occur prior to performing other trial-related eligibility assessments.

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

[f] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

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

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] On Day 15 of the first 3 cycles, only ALT, AST, total bilirubin, direct bilirubin need to be assessed.

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] A single 12-lead ECG should be performed as specified, and additionally if clinically indicated during the study treatment period. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[n] Study drug compliance will be reviewed with the patient.

[o] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[p] At each subsequent tumor assessment, all measurable, and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[q] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[r] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[s] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[t] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

Appendix 13
Arm D: Ipatasertib in Patients with PTEN Loss/ Loss-of-Function or AKT Activating Mutation-Positive Tumors

14. ARM D: IPATASERTIB IN PATIENTS WITH PTEN LOSS/ LOSS-OF-FUNCTION OR AKT ACTIVATING MUTATION-POSITIVE TUMORS

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D.4 MATERIALS AND METHODS

D.4.1 Patients

To be enrolled in Arm D: ipatisertib treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

D.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm D: ipatisertib treatment:

- AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  – AKT1: E17K; L52R; Q79K
  – AKT2: E17K
  – AKT3: E17K; L51R; Q78K

  or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay (See Appendix 1 for details)
- ANC $\geq$ 1000/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib; and agreement to refrain from donating eggs during this same period. See detailed contraception requirements in Appendix 2.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

D.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm D: ipatasertib treatment:

- Triple negative adenocarcinoma of the breast (TNBC)

  TNBC tumors are defined as HER2 negative, estrogen receptor (ER) negative, and progesterone receptor (PgR) negative

  - ER or PgR negativity is defined as $<$ 1% of tumor cell nuclei immunoreactive to the respective hormonal receptor
  - HER2 negativity is assessed by IHC and/or in situ hybridization according to 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/recommendations-for-human-epidermal-growth-factor-2-testing-in-breast-cancer)
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade $\geq$ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Appendix 7)
- Uncontrolled pleural effusion, pericardial effusion, or ascites

D.4.2 Study Treatment

Study treatment in this arm will consist of ipatasertib.

D.4.2.1 Formulation and Packaging

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access.

For information on the packaging, handling and storage, see the Pharmacy Manual and Ipatasertib Investigator's Brochure.

D.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 28 day cycles.

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The tablets will be swallowed whole (not chewed) with 3 ounces (90 mL) of fluid. *Ipatasertib is recommended to be taken at least 2 hours after the last meal of the day, and patients should refrain from eating overnight*. Patients are required to receive prophylaxis (see Section D.5.2.2.1) with loperamide throughout the first cycle and at subsequent cycles as clinically indicated.

For ipatasertib doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 8 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for ipatasertib dosage modification and treatment interruption or discontinuation are provided in Section D.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

D.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

D.4.3.1 Permitted Therapy

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

- Oral contraceptives, as allowed per local guidelines
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy (see Section D.4.3.3). Treatment with ipatasertib should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For a single fraction of radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Prophylaxis use of loperamide is mandated in the first cycle and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Section D.5.2.1; please refer to that section for additional

details. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.

- Granulocyte colony-stimulating factor treatment is permitted. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are ≥60 years of age and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011)
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) is allowed. Both types of agents have potential immunomodulatory properties, but may be used as clinically indicated.
- Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per institutional practice. For example, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6).

D.4.3.2 Cautionary Therapy

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this

hold may be shorter, if discussed by the investigator with the Medical Monitor. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events (refer to Section D.5.2.2.6 and Section D.5.2.2.7 for details). All study treatment should be temporarily held during systemic corticosteroids treatment

D.4.3.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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

Therefore, strong CYP3A4/5 inhibitors or inducers or CYP3A4/5 substrates with a narrow therapeutic index should be avoided or used with caution (see Appendix 7). Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

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

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

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

D.4.3.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug−drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

D.4.3.3 Prohibited Therapy

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

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in Section D.4.3.2.1)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study 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 all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients who require short-term use of moderate CYP3A4 inhibitors may continue study treatment 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 [FDA]):
> http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

D.4.3.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit, potent CYP3A4 enzyme inhibitors, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

D.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the Arm D: Ipatasertib treatment. Refer to the schedule of activities (Section D.7) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation panel: INR and aPTT
- HbA1c, blood glucose (fasting)
- Amylase, lipase (fasting)
- Lipid panel (fasting): total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)

D.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm D: ipatisertib treatment.

D.5.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity. Refer to the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

D.5.2 Management of Patients Who Experience Adverse Events with Ipatasertib

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

D.5.2.1 Dose Modifications and Interruptions

Guidelines for dosage modification and treatment interruption or discontinuation are provided below.

Dose modifications will be performed as clinically appropriate based on the investigator's medical judgment. Details in this section can be used as guidance; however, only the specific dose levels shown should be used (Table 1).

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

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

If the patient does not tolerate the QD dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient (i.e., doses below 200 mg/day of ipatasertib) will be allowed (see Table 1). Dose re-escalation is not permitted for ipatasertib.

If needed, dose reductions may occur in decrements of 100 mg and no more than two dose reductions will be allowed. Accordingly, the possible daily doses of ipatasertib are shown in Table 1.

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

Table 1 Ipatasertib Dose Reductions

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

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib may be suspended for reasons other than toxicity (e.g., surgical procedures) in consultation with the Medical Monitor. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days, study drug may be restarted in consultation with the Medical Monitor.

D.5.2.2 Guidelines for Management of Specific Adverse Events Associated with Ipatasertib

Guidelines for management of specific adverse events are provided in the subsections below.

D.5.2.2.1 Diarrhea

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table 2. In this study, all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining computed tomography (CT) images or a stool culture for infectious workup [Clostridium difficile, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines.

Dose reductions of ipatasertib will be by one level at a time (e.g., 400 to 300 mg; 300 to 200 mg) as outlined in Section D.5.2.1 and Table 1. If Grade $\geq$2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued.

Table 2 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients are mandated to receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance. If there are clinical concerns that preclude the use of loperamide prophylaxis in Cycle 1, discussion with the Medical Monitor is required. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12hour diarrhea free interval. • Dietary modifications, such as avoiding any lactosecontaining foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or lowcalorie- drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactosecontaining foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or lowcalorie- drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib 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 1) for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Table 2 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 3 Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level (see Table 1) when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level (see Section D.5.2). • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib.

ADL = activities of daily living; BID = twice a day; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v5.0, a disorder characterized by frequent and watery bowel movements.

D.5.2.2.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined Table 3 and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and the investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Table 3 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) [a]	• Monitor fasting glucose per protocol • Consider initiating home glucose monitoring
Fasting glucose value > 160 to 250 mg/dL (> 8.9–13.9 mmol/L) [a]	• Interruption of ipatasertib until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Initiate home glucose monitoring • Start oral anti-diabetic medications (e.g., metformin). • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table 1). • If the patient previously has not been receiving any oral antidiabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) [a]	• Interrupt ipatasertib dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Initiate home glucose monitoring • Treat hyperglycemia as medically appropriate. Start (or increase dose of) oral antidiabetic medications (e.g., metformin). • 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 fasting hyperglycemia ≥ 250 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level when treatment is restarted.
Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences [a]	• Interrupt ipatasertib dosing until resolution to ≤ 160 mg/dL. • Treat hyperglycemia as medically appropriate. • Initiate home glucose monitoring • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduce ipatasertib by one dose level if and when treatment is restarted. • If hyperglycemia > 500 mg/dL recurs, permanently discontinue ipatasertib.

ULN = upper limit of normal.

[a] For all grades, the patient should receive education on a diabetic diet.

D.5.2.2.3 Neutropenia and/or Thrombocytopenia

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection

and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib Table 4.

Table 4 Neutropenia and Thrombocytopenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib may be continued at the original dose
Grade 3	• Ipatasertib should be held until recovery to Grade 1 and if clinically appropriate based on the investigator's medical judgment to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: If recovery is to Grade 1, resume the original dose. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. If recovery is to Grade 2, follow the guidance above. – Recurrent episode: Ipatasertib should be reduced by one dose level when treatment is restarted. If patient has had more than three Grade 3 neutropenia episodes on study, the patient may continue to receive ipatasertib following discussion with the Medical Monitor. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient may continue ipatasertib following discussion with the Medical Monitor.
Febrile neutropenia and Grade 4 neutropenia	• Ipatasertib should be held until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. First episode: Ipatasertib should be reduced by one dose level when treatment is restarted. Recurrent episode: Ipatasertib should be discontinued. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue ipatasertib treatment.

G-CSF= granulocyte colony-stimulating factor.

D.5.2.2.4 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or

metoclopramide per institutional guidelines; see Table 5). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in Section D.5.2, Table 1, and Table 5.

Table 5 Nausea and Vomiting Management Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥3	• Interrupt ipatasertib until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level (see Table 1) when treatment is restarted.

D.5.2.2.5 Hepatotoxicity

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3×ULN *(or baseline, if baseline was abnormal)* and total bilirubin greater than 2×ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table 6)

Table 6 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > baseline –3.0 × ULN *if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal* or T bilirubin > baseline –1.5 × ULN *if baseline was normal; > 1.0–1.5 × baseline if baseline was abnormal*	• Continue study drugs.
Grade 2 AST or ALT > 3.0–5.0 × ULN *if baseline was normal; 3.0–5.0 × baseline if baseline was abnormal* or T bilirubin > 1.5–3.0 × ULN *if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal*	• Continue study drugs. • The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 AST or ALT > 5.0–20.0 × ULN *if baseline was normal; 5.0–20.0 × baseline if baseline was abnormal* or T bilirubin > 3.0–10.0 × ULN *if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal*	• Immediately interrupt ipatasertib. • On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/ at previous dose level (refer to Table 1) • Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. • If another Grade 3 event occurs, interrupt ipatasertib/. On return of LFTs to baseline or AST and ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN levels, restart ipatasertib/, reducing the dose by one level • Further Grade 3 occurrences must result in permanent discontinuation of ipatasertib.
Grade 4 AST or ALT > 20.0 × ULN *if baseline was normal; > 20.0 × baseline if baseline was abnormal* or T bilirubin > 10.0 × ULN *if baseline was normal; > 10.0 × baseline if baseline was abnormal*	• Permanently discontinue ipatasertib.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

D.5.2.2.6 Rash

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in Table 7 (see Section D.5.2 and Table 1 for dose modifications).

Table 7 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose (see Table 1). • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

D.5.2.2.7 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 8).

Table 8 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Consider resuming ipatasertib at same dose level or one dose level below (see Table 1) per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose (see Table 1). • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Resume ipatasertib at one dose level below previous dose (see Table 1) per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

D.5.2.2.8 Mucositis

Mouthwash such as magic mouthwash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage

modification guidelines for mucositis attributable to study treatment are outlined in Table 9.

Table 9 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level (see Table 1).
Grade ≥ 3	• Hold ipatasertib until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level (see Table 1). • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently ipatasertib.

D.5.2.2.9 *Dyslipidemia*

Use of lipid-lowering therapy for patients experiencing Grade ≥ 2 elevations may be initiated per institutional standard of care.

D.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients taking ipatasertib:

- Grade ≥ 3 fasting hyperglycemia
- Grade ≥ 3 hepatotoxicity
- Grade ≥ 3 ALT/AST elevations
- Grade ≥ 2 colitis/enterocolitis
- Grade ≥ 3 diarrhea
- Grade ≥ 3 rash
- Grade ≥ 2 pneumonitis

D.5.4 Selected Adverse Events

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

- Diarrhea

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

D.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-Treatment Screening	Treatment Period		End Of Treatment Visit [b]
Day And Study Cycle		Day 1 Of Each Cycle	Other Days As Specified	
Day (Window)	–28 *to* –1 [a]	(±3)	(±3)	≤ 28 Days *After* Last Study Dose
Informed consent [d]	x			
Documentation of positive AKT activating mutation or PTEN loss/loss of function status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
Coagulation panel [l]	x			x
Fasting lipid panel, amylase, lipase [m]	x	x		x
Fasting HbA_{1C} [m]	x	x		x
Fasting blood glucose [n]	x	x	Weekly during C1	x
ECHO or MUGA [o]	x	As clinically indicated		
Response assessments [p, q]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [r]		Submit within 21 days of C1, D1		
Whole blood samples [s]	x		See footnote s	
Study drug compliance assessment [t]		x		x

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Assessments	Pre-Treatment Screening	Treatment Period		End Of Treatment Visit [b]
Day And Study Cycle		Day 1 Of Each Cycle	Other Days As Specified	
Day (Window)	–28 *to* –1 [a]	(±3)	(±3)	≤ 28 Days *After* Last Study Dose
Study drug dispensing		x		
Prophylaxis anti-diarrheal [u]		Every day of cycle 1 and as clinically indicated		
Adverse events [v]	x	Collected on an ongoing basis		*x* [v]
Concomitant Medications [w]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1, with the exception of glucose, which should be drawn within 3 days prior. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive AKT gene activating mutations or PTEN loss or loss of function status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1, with the exception of glucose, which should be drawn within 3 days prior. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] Fasting lipid panel (cholesterol, triglyceride, HDL, and LDL), amylase, lipase and HbA1c will be assessed after ≥8 hours of fasting. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[n] Samples should be assessed weekly during the first Cycle and D1 at every other cycle. Mid-cycle fasting glucose levels may be obtained by glucometer (fingerstick). If measurements are done at home, phone visits with site staff should be conducted to review results and assess any potential signs or symptoms of hyperglycemia.

[o] LVEF assessment by ECHO or MUGA to be performed at screening and as clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[p] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[q] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[r] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[s] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[t] Study drug compliance will be reviewed with the patient.

[u] Loperamide 2 mg BID or equivalent or per local institutional guideline 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.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

D.7 REFERENCES

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Appendix 14
Arm E: Atezolizumab plus Chemotherapy in Patients with TMB-H/MSI-H/dMMR-Positive Tumors

15. ARM E: ATEZOLIZUMAB PLUS CHEMOTHERAPY IN PATIENTS WITH TMB-H/MSI-H/DMMR-POSITIVE TUMORS

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E.4 MATERIALS AND METHODS

E.4.1 Patients

To be enrolled in Arm E: atezolizumab plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

E.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm E: atezolizumab plus chemotherapy treatment:

- Documentation of one of the following biomarkers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified assay (tissue or blood):
  - Tumor mutational burden-high (TMB-H), defined as ≥10 mutations per megabase as determined by a tissue-based NGS assay
  - Microsatellite instability high (MSI-H)
  - Deficient mismatch repair (dMMR)
- ANC ≥ 1500/μL within 14 days prior to initiation of study treatment
- Lymphocyte count ≥500/μL
- For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period. Please see Appendix 2 for complete details on contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for 3 months after the last dose of chemotherapy and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

E.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm E: atezolizumab plus chemotherapy treatment:

- Primary CNS tumors with any of the following characteristics:

  - History of intracranial hemorrhage or spinal cord hemorrhage
  - Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1
- Metastases to the midbrain, pons, medulla, or spinal cord
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ upper limit of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  - 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.

- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti-CTLA-4 treatment may be enrolled, provided the following requirements are met:

  - Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment
  - No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events [NCI CTCAE] Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

E.4.2 Study Treatment

Study treatment in this arm will consist of atezolizumab in combination with either docetaxel, paclitaxel, or capecitabine chemotherapy, as determined by the investigator.

E.4.2.1 Formulation and Packaging

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.

Chemotherapy will consist of either docetaxel, paclitaxel, or capecitabine, as determined by the investigator and will be used in commercially available formulations.

For information on the formulation and handling of docetaxel, paclitaxel, and capecitabine, refer to the respective package insert.

E.4.2.2 Study Treatment Dosage, Administration, and Compliance

Study treatment will be administered in 21-day cycles. Atezolizumab should be administered prior to chemotherapy on days when both are administered.

If a delay in administration of either agent is necessary, reasonable effort should be made to keep the administration synced if clinically feasible (e.g., briefly delay administration of the other agent). A cycle should be considered to start when any drug is administered.

If atezolizumab is discontinued, chemotherapy can be continued if the patient is likely to derive clinical benefit, as determined by the investigator. If chemotherapy is

discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

E.4.2.2.1 Dosage, Administration, and Compliance for Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit in consultation with the Medical Monitor, see Section 3.1.2 for treatment beyond disease progression).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a] • 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. [a] • 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 measured within 60 minutes prior to the infusion. [a] • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section E.5.2.2.7.

No dose reductions for atezolizumab are allowed. See Section E.5.2 for management guidelines.

E.4.2.2.2 Dosage, Administration, and Compliance for Docetaxel, Paclitaxel, and Capecitabine

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

E.4.3 Concomitant Therapy

E.4.3.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- 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 E.4.3.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD 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 may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment in consultation with the Medical Monitor. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.
- 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 (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section E.4.3.2 and Section E.4.3.3) 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 6).

E.4.3.2 Cautionary Therapy

E.4.3.2.1 Corticosteroids and TNF-α Inhibitors

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

Patients with primary CNS tumors can be receiving concurrent treatment with corticosteroids in consultation with the Medical Monitor. Patients must be receiving a stable or decreasing dose for ≥5 days prior to the baseline magnetic resonance imaging (MRI) scan and at the time of drug initiation.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section E.5.2 for details).

E.4.3.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

E.4.3.3 Prohibited Therapies

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 within 3 weeks prior to starting study treatment and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with

the exception of palliative radiotherapy and local therapy under certain circumstances (see Section E.4.3.1 for details).

- Investigational therapy 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 atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Any prohibited therapies in accordance with the local label for applicable chemotherapy

E.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients receiving atezolizumab. Refer to the schedule of activities (Section E.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)

E.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm E: atezolizumab plus chemotherapy treatment.

E.5.1 Risks Associated with Atezolizumab plus Chemotherapy

E.5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis,

Guillain-Barré syndrome, myasthenic syndrome 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 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

E.5.1.2 Risks Associated with Docetaxel, Paclitaxel, and Capecitabine

Docetaxel has been associated with risks such as the following: infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. For more details regarding the safety profile of docetaxel, refer to the prescribing information for docetaxel.

Paclitaxel has been associated with risks such as the following: Bone marrow suppression, neutropenia, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Additionally reported adverse events which were less common are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test (LFT) elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis. For more details regarding the safety profile of paclitaxel, refer to the prescribing information for paclitaxel.

Capecitabine has been associated with risks such as the following: diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. For more details regarding the safety profile of capecitabine, refer to the prescribing information for capecitabine.

E.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

E.5.2.1 Dose Modifications and Interruptions

E.5.2.1.1 Dose Modifications and Interruptions for Atezolizumab

No dose reductions for atezolizumab are allowed.

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 the equivalent of ≤10 mg/day oral

prednisone before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, 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.

E.5.2.1.2 Dose Modifications and Interruptions for Chemotherapy

Dose modifications and interruptions for docetaxel, paclitaxel, and capecitabine should be done according to standard medical practice and in accordance with the respective packaging insert.

E.5.2.2 Guidelines for Management of Specific Adverse Events Associated with Atezolizumab

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

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

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *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. 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 hormone-replacement therapy.*
- The investigator should consider the benefit–risk balance for a given patient 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.

E.5.2.2.1 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.

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. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 2.

Table 2 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 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 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. • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/ 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.

BAL = bronchoscopic alveolar lavage.

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

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

E.5.2.2.2 Hepatic Events

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 3.

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.

Table 3 Management Guidelines for Hepatic Events

Event	Management
Guidelines for patients without hepatocellular carcinoma	
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
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]

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 the equivalent of ≤ 10 mg/day oral prednisone. 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 3 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for patients without hepatocellular carcinoma (cont.)	
Hepatic event, Grade 3 or 4	• 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 Grade 1 or better, taper corticosteroids over ≥ 1 month.
Guidelines for patients with hepatocellular carcinoma	
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]

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 the equivalent of ≤ 10 mg/day oral prednisone. 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 3 Management Guidelines for Hepatic Events (cont.)

Guidelines for patients with hepatocellular carcinoma (cont.)	
Event	Management
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.

LFT = liver function test; ULN = upper limit of normal.

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

E.5.2.2.3 Gastrointestinal Events

Management guidelines for diarrhea or colitis are provided in Table 4.

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 4 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]

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 the equivalent of ≤10 mg/day oral prednisone. 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 4 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
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]
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; IV=intravenous.

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

E.5.2.2.4 Endocrine Events

Management guidelines for endocrine events are provided in Table 5.

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

Table 5 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 and 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.
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.*

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. 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 5 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to 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, Grades 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • 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.
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.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. 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 5 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 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 if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *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 if clinically indicated.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. 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.

E.5.2.2.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 6.

Table 6 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 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 the equivalent of ≤ 10 mg/day oral prednisone. 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.

E.5.2.2.6 *IMMUNE-MEDIATED CARDIAC EVENTS*

Management guidelines for cardiac events are provided in Table 7.

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 and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis *or associated with pericarditis (see section on pericardial disorders below)* 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 (ECHO), 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 7.

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 7. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 7 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.

E.5.2.2.7 Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an 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 medical management of IRRs and CRS are provided in Table 8.

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 8 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 blowby	• 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 8 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, nonrebreather 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 8 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 v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic 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) for information on experimental treatments for CRS.

E.5.2.2.8 Pancreatic Events

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 9.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 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; ULN=upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 9 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 the equivalent of ≤ 10 mg/day oral prednisone. 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.

E.5.2.2.9 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 10.

Table 10 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 the equivalent of ≤ 10 mg/day oral prednisone. 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 10 Management Guidelines for Dermatologic Events (cont.)

Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. 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.

E.5.2.2.10 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 11, *with specific guidelines for myelitis provided in* Table 12.

Table 11 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	• *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 atezolizumab, 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. [c] • 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 the equivalent of ≤ 10 mg/day oral prednisone. 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 12 *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.*

E.5.2.2.11 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 13.

Table 13 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.

E.5.2.2.12 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 nonsteroidal 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 14.

Table 14 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. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

E.5.2.2.13 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 15.

Table 15 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 the equivalent of ≤ 10 mg/day oral prednisone. 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 15 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *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 Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
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 the equivalent of ≤ 10 mg/day oral prednisone. 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.

E.5.2.2.14 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 < 9 g/dL (< 10 g/dL for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L
  - ANC $< 1000/\mu$L
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 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
  - 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 16.

Table 16 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.

E.5.2.3 Guidelines for Management of Adverse Events Associated with Chemotherapy

Toxicities associated or possibly associated with docetaxel, paclitaxel, or capecitabine treatment should be managed according to standard medical practice and in accordance with the respective packaging insert.

E.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients receiving atezolizumab:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- *Myelitis*
- *Facial paresis*

E.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 TO −1 [A]	(±3)	(±3)	≤28 days *after* last study dose
Informed consent [d]	x			
Documentation of TMB-H/ MSI-H/dMMR status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation panel [m]	x			x
Thyroid function test (TSH, free T3 [or total T3], free T4)	x	x		x
ECHO/MUGA [n]	x	As clinically indicated		x
Atezolizumab administration [o]		x		
Chemotherapy administration [p]		x	see footnote p	
Response Assessment [q, r]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [s]		Submit within 21 days of Cycle 1 Day 1		
Whole blood samples [t]	x		See footnote t	
Adverse events [u]	x	Collected on an ongoing basis		*x* [u]
Concomitant medications [v]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease;; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the chemistry panel and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post- chemotherapy discontinuation or 90 days post-atezolizumab discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of TMB-H/MSI-H/dMMR status should occur prior to performing other trial-related eligibility assessments. TMB-H should be determined using a tissue-based NGS assay.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a

serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 3 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes aPTT and INR.

[n] LVEF assessment by ECHO or MUGA to be performed at screening*, at end of treatment,* and as clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[o] The initial infusion 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.

[p] Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

[q] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[r] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors) or loss of clinical benefit (with Medical Monitor consultation; see Section 3.1.2), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[s] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[t] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of chemotherapy or 90 days after the final dose of atezolizumab, whichever is longer. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-chemotherapy discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[v] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study treatment.

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Appendix 15
Arm F: Trastuzumab Emtansine Plus Atezolizumab in Patients with ERBB2 Gene Amplification- or Mutation-Positive Tumors

16. ARM F: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH ERBB2 GENE AMPLIFICATION- OR MUTATION-POSITIVE TUMORS

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F.4 MATERIALS AND METHODS

F.4.1 Patients

To be enrolled in Arm F: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

F.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- ERBB2 mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T
  - Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell

- ANC ≥ 1200/μl within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizuamb, whichever is longer; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details regarding requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

F.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 as determined by a tissue-based NGS assay, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin > 500 mg/m^2
  - Liposomal doxorubicin > 500 mg/m^2
  - Epirubicin > 720 mg/m^2
  - Mitoxantrone > 120 mg/m^2
  - Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg)

  - Inadequate left ventricular ejection fraction at baseline, $<$50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - History of symptomatic congestive heart failure Grade $\geq$3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  - History of decrease in left ventricular ejection function to $<$40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade $\geq$2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$1.5 mmol/L, calcium $>$12 mg/dL, or corrected calcium $>$upper limit of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade $\geq$3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  - 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

- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain
  - Patients requiring 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 ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation
  - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha (TNF-α) agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

F.4.2 Study Treatment

Study treatment in this arm will consist of atezolizumab in combination with trastuzumab emtansine.

F.4.2.1 Formulation and Packaging

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.

Trastuzumab emtansine is provided as a lyophilized product in either 15-mL or 20-mL single-use vials which contain enough product to deliver 100 mg or 160 mg, respectively, of trastuzumab emtansine. The lyophilized form of the product is provided for reconstitution to a liquid concentrate using sterile water for injection. After reconstitution, both the 15-mL and 20-mL vials contain 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 6% w/v sucrose, and 0.02% (w/v) polysorbate 20. The reconstituted product contains no preservative and is intended for single use only. The density of the drug product after reconstitution is 1.026 g/mL.

For information on the formulation and handling of trastuzumab emtansine, see the pharmacy manual and the Trastuzumab Emtansine Investigator's Brochure.

F.4.2.2 Dosage, Administration, and Compliance

Atezolizumab will be administered first followed by trastuzumab emtansine.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a] • 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. [a] • 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 measured within 60 minutes prior to the infusion. [a] • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section E.5.2.2.7 for atezolizumab.

No dose modification for atezolizumab is allowed.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity (or loss of clinical benefit with Medical Monitor consultation when given in combination with atezolizumab; Section 3.1.2 for treatment beyond disease progression). The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes $>$10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. The calculated total dose may be rounded to the nearest milligram.

Trastuzumab emtansine infusions will be administered per the instructions outlined in Table 2.The initial dose will be administered over 90 minutes. Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must

be assessed predose and postdose. Following the initial dose, patients will be observed for at least 90 minutes. Subsequent doses of trastuzumab emtansine may be administered over 30 minutes. Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section F.5.2.2.4.

If a delay in administration of either agent is necessary, reasonable effort should be made to keep the administration synced if clinically feasible (e.g., briefly delay administration of the other agent). A cycle should be considered to start when any drug is administered.

Table 2 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • Administer the initial dose as a 90-minute intravenous infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions • Patient should be observed during the infusions and for at least 30 minutes after infusion.

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

F.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

F.4.3.1 Permitted Therapy

Use of the following therapies is permitted during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)

- Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section F.4.3.2)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for the prevention or delay of skeletal complications, and palliation of bone pain in patients with documented bone metastases. Use bisphosphonates or other agents for hypercalcemia or malignancy is prohibited and patients requiring such treatment should be evaluated for progressive disease.
- Erythropoiesis-stimulating agents or granulocyte colony-stimulating factors
- Radiation therapy for the treatment of bone pain for bone metastases in the absence of progressive disease
- Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, as clinically indicated.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

F.4.3.2 Prohibited Therapy

Use of the following therapy is prohibited during study treatment:

- Any systemic therapy intended for the treatment of the disease under study, including any other investigational agent
- Concomitant use of potent cytochrome (CYP) P450 3A4/5 inhibitors (such as ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4/5. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.
- Any hormonal therapy used for the treatment of the disease under study. Patients who require the use of these agents will be discontinued from study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see

Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited within 2 weeks prior to the initiation of study treatment and during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed.

F.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients receiving trastuzumab emtansine plus atezolizumab. Refer to the schedule of activities (Section F.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation: INR and aPTT
- Thyroid function test (thyroid-stimulating hormone [TSH], free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)

F.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm F: trastuzumab emtansine plus atezolizumab treatment.

F.5.1 Risks Associated with Trastuzumab Emtansine plus Atezolizumab

F.5.1.1 Risks Associated with Trastuzumab Emtansine

Trastuzumab emtansine has been associated with risks such as the following: hepatotoxicity, (predominantly in the form of asymptomatic increases in the concentrations of serum transaminases; serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver), left ventricular dysfunction, infusion-related reaction (IRR), hypersensitivity, hemorrhagic events, (including CNS, respiratory, and gastrointestinal hemorrhage), thrombocytopenia, peripheral neuropathy, reactions secondary to extravasation, and interstitial lung disease (including pneumonitis). Refer to the Trastuzumab Emtansine Investigator's Brochure for a description of all anticipated safety risks for trastuzumab emtansine.

F.5.1.2 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 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Suggested workup and management guidelines for overlapping toxicities between atezolizumab and trastuzumab emtansine, pulmonary and hepatic events, are provided in Section F.5.2.4.

F.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

F.5.2.1 Dose Modifications and Interruptions

F.5.2.1.1 Dose Modifications and Interruptions for Trastuzumab Emtansine

For adverse events not listed below in Section F.5.2.2 the following guidance should be used with regards to dose delays and modifications:

- For Grade 3 non-hematologic adverse events not adequately managed by standard medical intervention or for any Grade 4 non-hematologic adverse event, study

treatment should be held until recovery to Grade ≤1. A maximum dose delay of 42 days for the last administered dose of study drug will be allowed.

- If withheld for <42 days, trastuzumab emtansine may be resumed at either the same dose level as before or at one dose level lower (see Table 3), at the discretion of the investigator. Subsequent cycles should remain every 21 days.
- Dose re-escalation is not permitted for trastuzumab emtansine.
- Resuming trastuzumab emtanzine after 42 days may be considered in exceptional circumstances and should be done in consultation with the Medical Monitor.

Table 3 Recommended Dose Reduction Schedule for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Permanently discontinue

F.5.2.1.2 Dose Modifications and Interruptions for Atezolizumab

No dose reductions for atezolizumab are allowed. Interruptions to atezolizumab treatment are described in Section E.5.2.1.1.

F.5.2.2 Guidelines for Management of Specific Adverse Events for Trastuzumab Emtansine

F.5.2.2.1 Hepatotoxicity

Hepatotoxicity is an overlapping toxicity for trastuzumab emtansine and atezolizumab. Management guidelines are provided in, Section F.5.2.4.2.

F.5.2.2.2 Pulmonary Toxicity

Pulmonary Toxicity is an overlapping toxicity for trastuzumab emtansine and atezolizumab. Management guidelines are provided in Section F.5.2.4.1.

F.5.2.2.3 Cardiotoxicity

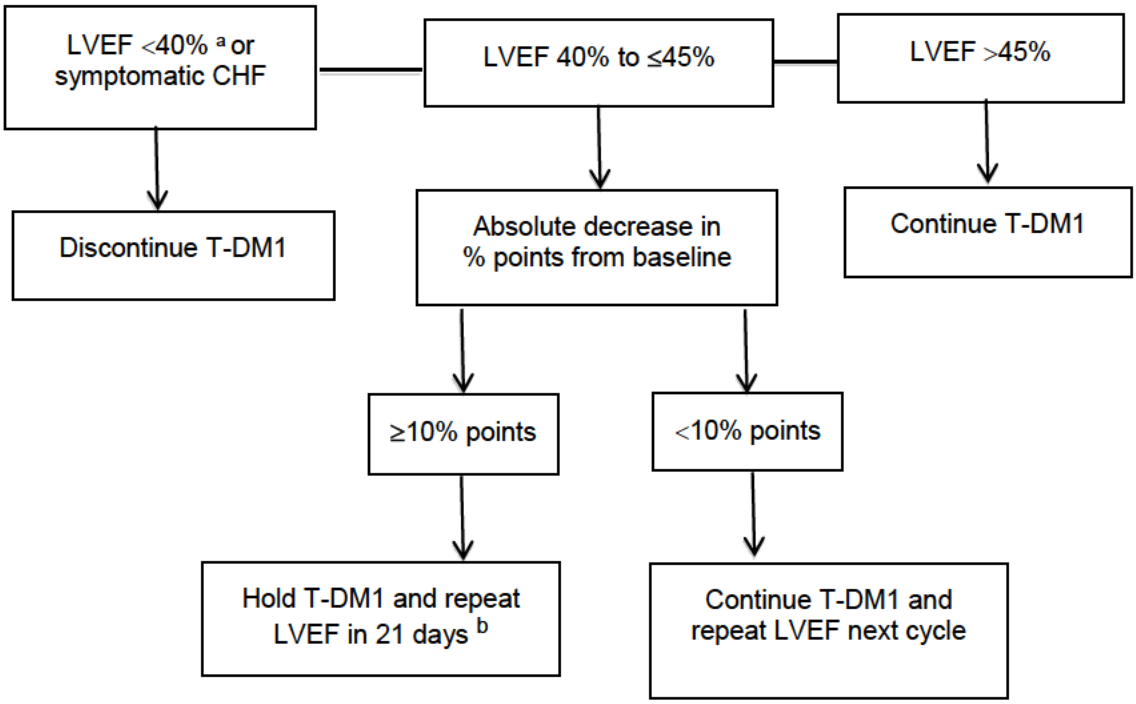
Patients without significant cardiac history and with a baseline LVEF of ≥50% as determined by ECHO or MUGA scan are eligible for arm participation. Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in this arm. Assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed

>28 days before last study treatment administration and if no post-treatment evaluation was performed (see Section F.6).

Figure 1 summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in patients. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 1 or asymptomatic declines in LVEF. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed decrease of LVEF to <40% is documented (with a confirmation assessment carried out within 21 days). For patients whose LVEF decreases to values of 40%–45% with an absolute decrease in LVEF of ≥10% points from baseline, trastuzumab emtansine dose should be held. For these patients, the LVEF measurement should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if the LVEF has not recovered to within a 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain LVEF, the patient should be discontinued from all study treatment.

Figure 1 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Patients



CHF = congestive heart failure; LVEF = left ventricular ejection fraction; T-DM1 = trastuzumab emtansine.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] LVEF <40% should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if LVEF <40% is confirmed. Trastuzumab emtansine should be held while the confirmatory LVEF measurement is obtained.

[b] After a second consecutive confirmatory measurement is obtained, trastuzumab emtansine treatment should be discontinued if the ≥10% absolute LVEF decrease from baseline is confirmed.

F.5.2.2.4 Infusion-Related Reactions and Hypersensitivity Reactions

See Table 4 for management guidelines for trastuzumab emtansine–associated infusion-related reactions and hypersensitivity reactions.

Table 4 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.

F.5.2.2.5 Hematologic Toxicities

See Table 5 for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 5 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade 2 thrombocytopenia (50,000 to 75,0000/μL)	Assess platelet counts weekly or as medically indicated until recovery. Withhold study treatment until Grade ≤ 1. Resume treatment without dose reduction.
Grade 3 thrombocytopenia (25,000 to < 50,000/μL)	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/μL) at any time	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade ≥ 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

F.5.2.2.6 Neuropathy

See Table 6 for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 6 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade ≥ 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

F.5.2.3 Guidelines for Management of Specific Adverse Events Associated with Atezolizumab

Guidelines for management of specific adverse events associated with atezolizumab can be found in Section E.5.2.2.

F.5.2.4 Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

The following adverse events are potential overlapping toxicities associated with combination use of trastuzumab emtansine and atezolizumab: pulmonary and hepatic events.

F.5.2.4.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates.

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:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study, and will also have CT scans of the chest at every tumor assessment. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* See Table 7 for management guidelines for pulmonary events and pneumonitis.

In this study, atezolizumab and trastuzumab emtansine are discontinued for all grades of interstitial lung disease and pneumonitis.

Table 7 Management Guidelines for Interstitial Lung Disease and Pneumonitis

Severity	Trastuzumab Emtansine	Atezolizumab
Grade 1 – 4	Discontinue trastuzumab emtansine treatment.	Discontinue atezolizumab treatment

F.5.2.4.2 Hepatic Events

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Liver function will be monitored throughout study treatment.

While on this study, patients who present 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.

If outcome of LFTs is worsening, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for worsening outcome of LFTs. Antinuclear antibody, perinuclear antineutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. See Table 8 for management guidelines for atezolizumab and trastuzumab emtansine hepatic events.

See Table 8 for Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events. See Table 9 for dose modifications of trastuzumab emtansine for hyperbilirubinemia.

> Note: No dose modification for atezolizumab is indicated on the basis of hyperbilirubinemia alone.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Atezolizumab	Trastuzumab Emtansine
ALT or AST increase that meets Hy's law criteria: ALT or AST $>3\times$ ULN, in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue atezolizumab treatment.	Discontinue trastuzumab emtansine treatment.
Grade 1 *AST or ALT > ULN–3.0 × ULN if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal*	Treat at the same dose level. Continue LFT monitoring.	Treat at the same dose level.
Grade 2 *AST or ALT >3.0–5.0 × ULN if baseline was normal; >3.0–5.0 × baseline if baseline was abnormal*	Withhold atezolizumab dose. If persists >5–7 days: Consider starting 1–2 mg/kg/day prednisone or equivalent per day; when recover to Grade ≤ 1, taper steroids over ≥ 1 month. Resume therapy when systemic steroid dose is $\leq$ 10mg oral prednisone equivalent per day and resume when recovery to Grade ≤ 1 at same dose within 12 weeks. Permanently discontinue atezolizumab and contact the Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.	Treat at the same dose level.

GI = gastrointestinal; LFT = liver function test; NRH = Nodular Regenerative Hyperplasia; TNF = tumor necrosis factor; ULN = upper limit of normal.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab	Trastuzumab Emtansine
Grade 3 *AST or ALT* *> 5.0–20.0 × ULN if baseline was normal;* *> 5.0–20.0 × baseline if baseline was abnormal*	Discontinue atezolizumab dose. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab treatment is discontinued.	Withhold trastuzumab emtansine dose. Do not administer trastuzumab emtansine until recovery to Grade ≤ 2, and then resume with dose reduction by one level. Discontinue trastuzumab emtansine treatment if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.
Grade 4 *AST or ALT > 20.0 × ULN if baseline was normal;* *> 20.0 × baseline if baseline was abnormal*	Discontinue atezolizumab treatment. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab treatment is discontinued.	Discontinue trastuzumab emtansine treatment. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.

GI = gastrointestinal; LFT = liver function test; NRH = Nodular Regenerative Hyperplasia; TNF = tumor necrosis factor; ULN = upper limit of normal.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab	Trastuzumab Emtansine
NRH If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered.	Discontinue atezolizumab treatment	Discontinue trastuzumab emtansine treatment and have the patient evaluated by a hepatologist.

GI = gastrointestinal; LFT = liver function test; NRH = Nodular Regenerative Hyperplasia; TNF = tumor necrosis factor; ULN = upper limit of normal.

Table 9 Trastuzumab Emtansine Dose Modification Guidelines for Hyperbilirubinemia

Severity	Action to be Taken
Grade 2 *Total bilirubin > 1.5–3.0 × ULN if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal*	Withhold until total bilirubin recovers to Grade ≤ 1 and then resume at the same dose level.
Grade 3 *Total bilirubin > 3.0 - 10.0 × ULN if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal*	Withhold until total bilirubin recovers to Grade ≤ 1 and then resume by one dose level reduction.
Grade 4 *Total bilirubin > 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal*	Discontinue trastuzumab emtansine treatment.

ULN = upper limit of normal.

F.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, for Arm F, the following adverse events are required to be reported by the investigator immediately:

Atezolizumab

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

Trastuzumab Emtansine

- Not Applicable

F.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive ERBB2 gene mutation or amplification by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation Panel [m]	x			x
Thyroid function test (TSH, free T3 [or total], and free T4) [n]	x	C1, D1 and every 4 cycles thereafter		
ECHO or MUGA [o]	x	As clinically indicated	C1, D15 and every 4 cycles thereafter	x [o]
Atezolizumab administration [p]		x		
Trastuzumab emtansine administration [q]		x		
Response Assessments [r, s]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [t]		Submit within 21 days of C1, D1		
Whole blood samples [u]	x		see footnote u	

Arm F: Trastuzumab Emtansine plus Atezolizumab in Patients With ERBB2 Mutant-Positive Tumors

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Adverse events [v]	x	Collected on an ongoing basis		*x* [v]
Concomitant Medications [w]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; PET=positron emission tomography; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC, chemistry panel, and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-trastuzumab emtansine discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ERBB2 gene mutation or amplification without known TMB-H/MSI-H/dMMR status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes INR and aPTT.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] LVEF assessments will occur during the screening period, and on Day 15 of Cycle 1, every fourth cycle thereafter (e.g. C5D15, C9D15, etc.). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[p] Atezolizumab will be administered first by IV infusion at a dose of 1200 mg on Cycle 1, and on Day 1 of each 21-day cycle thereafter. For the first infusion of atezolizumab, vital signs should be determined within 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes after the infusion, if clinically indicated. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.

[q] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Day 1 of Cycle 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-

related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[r] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[s] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (± 1) weeks for 3 evaluations, then every 12 (± 2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors)(or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[t] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[u] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of trastuzumab emtansine or 90 days after the final dose of atezolizumab, whichever is longer. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-trastuzumab emtansine discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study treatment.

F.7 REFERENCES

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Appendix 16
Arm G: PH FDC SC in Patients with ERBB2 Gene Amplification- or Mutation-Positive Tumors

17. ARM G: PH FDC SC IN PATIENTS WITH ERBB2 GENE AMPLIFICATION- OR MUTATION-POSITIVE TUMORS

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G.4 MATERIALS AND METHODS

G.4.1 Patients

To be enrolled in Arm G: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

G.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm G: PH FDC SC treatment:

- ERBB2 mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T
  - Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥1000/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (within 3 months) left ventricular ejection fraction (LVEF) ≥50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)

- For females of childbearing potential: Negative serum pregnancy test ≥ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details regarding contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC, and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

G.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm G: PH FDC SC treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 as determined by a tissue-based NGS assay, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- In addition to the core exclusion criterion for significant cardiovascular disease (see Section 4.1.2), patients will be excluded if they have any of the following:
  - High-risk arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia

demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome

- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for HBV
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC
- Current chronic daily treatment with corticosteroids (dose $>$ 10 mg methylprednisolone or equivalent excluding inhaled steroids)

G.4.2 Study Treatment

Study treatment in this arm will consist of PH FDC SC.

G.4.2.1 Formulation and Packaging

PH FDC SC will be provided in two configurations: a loading dose configuration and maintenance dose configuration as single vials:

- Loading dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 20 mL glass colourless vial contains 1200 mg of pertuzumab and 600 mg of trastuzumab in 15 mL of solution.
- Maintenance dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 15 mL colourless glass vial contains 600 mg of pertuzumab and 600 mg of trastuzumab in 10 mL of solution.

For information on the packaging, handling and storage of PH FDC SC, see the Pharmacy Manual and PH FDC SC Investigator's Brochure.

G.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 21-day cycles.

PH FDC SC is given as a fixed dose (i.e. non-weight based). Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had $\geq$6 weeks since a prior dose of Perjeta and Herceptin intravenous (IV) or PH FDC subcutaneous (SC) at study entry, or have had $\geq$6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

All PH FDC SC doses will be administered by SC injection by the investigator or their designee over 5–8 minutes at a rate of ≤2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Patients should be monitored for 30 minutes after their first PH FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10–15 minutes following subsequent administrations. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

No dose reductions are allowed for PH FDC SC. If an accidental overdose or medication error occurs, it 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 also be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section G.5.2.

G.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from seven days prior to initiation of study drug until 28 days after the final dose of study treatment. After this period until the end of the study, only medications used for the treatment of cancer will be reported. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

G.4.3.1 Permitted Therapy

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

- H_1-receptor or H_2-receptor antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics, beta blockers, calcium channel blockers, digoxin, thrombocyte aggregation inhibitors
- Analgesics / anti-inflammatories (e.g., paracetamol / acetaminophen, meperidine, opioids)
- Standard therapies for pre-existing medical conditions and medical or surgical complications
- Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) at the investigator's discretion
- Blood transfusions at the investigator's discretion

- Gonadotropin-releasing hormone agonists for fertility preservation
- Vitamin and mineral supplements
- Bone density modifying agents (to be used in accordance with the approved labelled indication and/or nationally recognized treatment guidelines)
- Any other medication not included in the list of prohibited medications

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per institutional 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 institutional 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 6).

G.4.3.2 Cautionary Therapy

Concomitant use of herbal therapies is not recommended because their pharmacokinetic profiles, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

G.4.3.3 Prohibited Therapy

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

- Any investigational therapy or agent (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment
- Any targeted anti-cancer treatment other than adjuvant hormone treatment, adjuvant radiotherapy or bone density modifying treatment (e.g., lapatinib, neratinib)
- Regular systemic treatment with steroids

  Short-term corticosteroid to treat and prevent allergic or infusion reactions are allowed however the dose must not exceed $>$20 mg/day of dexamethasone (or equivalent) for $>$7 consecutive days.

- Hormone-replacement therapy
- Use of erythropoiesis-stimulating agents (e.g., erythropoietin)
- Herbal remedies initiated for cancer treatment. Other herbal remedies are discouraged but permitted and must be reported on the appropriate eCRF.
- Topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators used with prophylactic intent are prohibited

Postmenopausal women with significant vaginal discomfort associated with anti-estrogen therapy may be considered for intermittent use of low-dose topical estrogens if non-prescription methods are unsuccessful at ameliorating symptoms.

G.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in Arm G: PH FDC SC. Refer to the schedule of activities (Section G.6) for arm-specific assessment timepoints.

Cardiac Function

Prior to study enrolment, patients must have an assessment for history of cardiac events, a physical examination, and an LVEF assessment (by ECHO or MUGA) to exclude any cardiac condition that would render them ineligible for participation in this trial. Cardiac function will be assessed locally according to the schedule of activities (Section G.6).

All patients must have an LVEF ≥50% by ECHO or MUGA scan in order to be eligible for the study. The same LVEF evaluation method should be used throughout the study for each patient and should be performed and assessed by the same assessor if possible. Results of LVEF assessments must be reviewed prior to study treatment administration on the scheduled visit day.

Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and patients in this study require LVEF assessment on more than four occasions within one year.

G.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm G: PH FDC SC treatment.

G.5.1 Risks Associated with PH FDC SC

PH FDC SC has been associated with risks such as the following: cardiomyopathy, embryo-fetal toxicity, pulmonary toxicity, alopecia, dry skin, rash, nausea, diarrhea, stomatitis, constipation, vomiting, dyspepsia, anemia, neutropenia, fatigue, mucosal inflammation, injection site reaction, pyrexia, dysgeusia, peripheral sensory neuropathy, headache, neuropathy peripheral, paresthesia, dizziness, weight decreased, myalgia, arthralgia, back pain, cough, epistaxis, dyspnea, upper respiratory tract infection, procedural pain, radiation skin injury, decreased appetite, insomnia, and hot flush. Refer to the PH FDC SC Investigator's Brochure for a detailed description of anticipated safety risks for PH FDC SC.

G.5.2 Management of Patients Who Experience Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

G.5.2.1 Dose Modifications and Interruptions for PH FDC SC

Dose modification of PH FDC SC is not permitted. The administration of PH FDC SC may be delayed to assess or treat adverse events, such as cardiac adverse events.

During the study treatment period, a dose delay of up to (and including) six weeks (i.e., up to and including nine weeks between doses) will be permitted to allow adverse event recovery to baseline. Following a dose delay of less than 3 weeks (i.e., <6 weeks between doses), study treatment does not need to be reloaded (only the maintenance doses needs to be given).

Patients receiving PH FDC SC with ≥ 6 weeks since their last PH FDC SC or Perjeta and Herceptin intravenous (IV) treatment must receive a loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab FDC SC before continuing with maintenance doses for subsequent administrations. Patients should be monitored for 30 minutes after their first PH FDC SC dose administration in the study and if a loading dose is required during the study. Patients should be monitored for 10–15 minutes following maintenance dose administrations.

If study treatment is withheld for more than two cycles (>9 weeks) because of toxicity, the patient should be discontinued from study treatment, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor consultation. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

G.5.2.2 Guidelines for Management of Specific Adverse Events Associated with PH FDC SC

Supportive care and medical management of adverse events are at the discretion of the investigator, unless specifically listed below.

G.5.2.2.1 Symptomatic LVSD and/or LVEF Decline

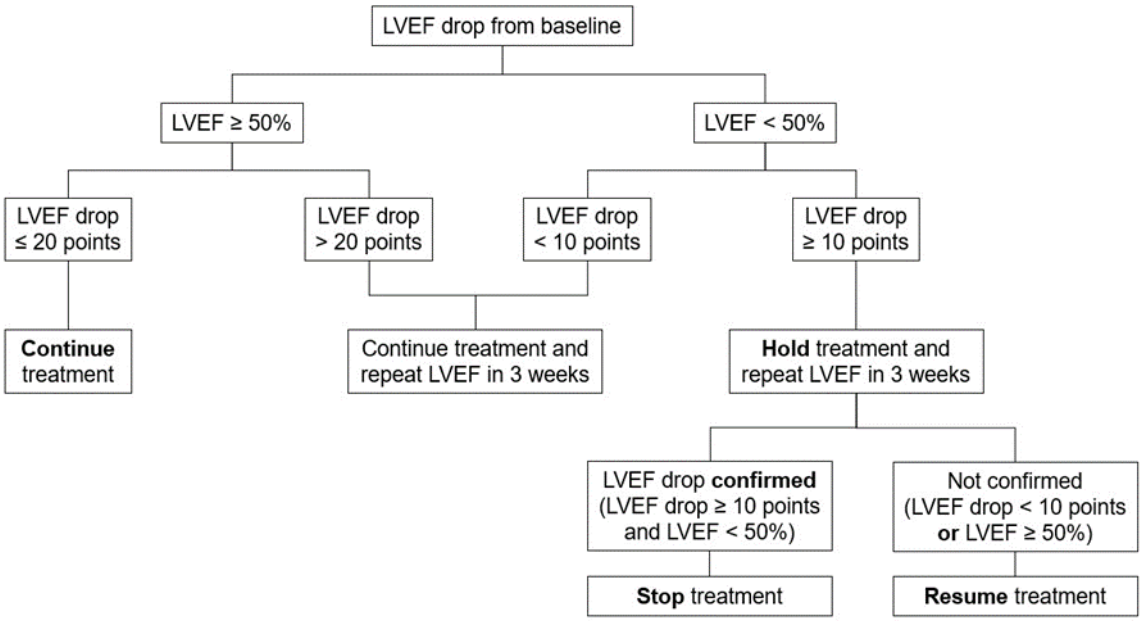
All patients must have a baseline LVEF $\geq 50\%$. LVEF will be monitored regularly according to the Schedule of Activities (see Section G.6). If an investigator is concerned that an adverse event may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within three weeks. Symptomatic LVSD (CHF) should be assessed as “heart failure” on the basis of NCI CTCAE v5.0 and NYHA classification (see Appendix 9). Symptomatic LVSD (CHF) should be treated and

monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist locally,

Figure 1 summarizes the management of study medication in patients who develop an asymptomatic decrease in LVEF. The decision to initiate study treatment and whether to continue or stop therapy should be based on two factors: measured LVEF and changes in LVEF from baseline. If a significant LVEF decrease occurs, this decrease should be confirmed by a second assessment within approximately 3 weeks showing also a significant decrease.

Heart failure and asymptomatic LVEF decline adverse events must be graded per NCI CTCAE v5.0 (see Appendix 9) and reported in the eCRF as described Section G.5.4.2.

Figure 1 Asymptomatic Decline in LVEF: Algorithm for Continuation and Discontinuation of Study Treatment



LVEF=left ventricular ejection fraction

Patients must have an LVEF ≥50% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) to be eligible for the study.

G.5.2.2.2 Hypersensitivity / Anaphylaxis and Administration-Related Reactions

Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with PH FDC SC, caution should be exercised as these have been associated with Perjeta IV in combination with Herceptin IV.

Study treatment administration should be stopped in subjects who develop dyspnea or clinically significant hypotension (defined per investigator's discretion).

Patients who experience any of the following events will be discontinued from study treatment:

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- Acute respiratory distress syndrome (ARDS)
- Bronchospasm

Patients who experience administration-related reactions (ARRs) may be managed by:

- Stopping the injection of PH FDC SC
- Supportive care with antihistamines, antipyretics, corticosteroids or epinephrine as appropriate at the investigator's discretion, as per institutional practice
- Subsequently pre-medicating with analgesia and antihistamines as per institutional practice

Patients should be monitored until complete resolution of signs and symptoms of any systemic reactions.

In order to be able to calculate time to onset of such reactions, the occurrence of associated adverse events must be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

All ARRs should be recorded as described in Section G.5.4.3.

G.5.2.2.3 Diarrhea

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g. loperamide) should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated.

G.5.2.2.4 Rash / Skin Reactions

Treatment recommendations for rash / skin reactions include topical or oral antibiotics, topical pimecrolimus, and topical steroids or systemic steroids (for severe reactions). These agents may be used in patients experiencing pertuzumab-related rash / skin reactions, as clinically indicated, although they have not been studied in this context.

G.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special

interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients in the Arm G: PH FDC SC.

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment

G.5.4 Reporting for Selected Adverse Events

Additional data will be collected for the selected adverse events described below.

G.5.4.1 Heart Failure

Symptomatic LVSD (referred to as heart failure) should be reported as an SAE. If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. Heart failure should be graded according to both NCI CTCAE and NYHA Class (see Appendix 9). Left ventricular ejection fraction results must also be reported.

Heart failure occurring during the study must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

G.5.4.2 Asymptomatic Declines in Left Ventricular Ejection Fraction

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

- An asymptomatic decline in LVEF of ≥ 10 percentage-points from baseline to an LVEF $< 50\%$ must be reported as an adverse event with the term of "ejection fraction decreased," as per NCI CTCAE v5.0 (see Appendix 9). In addition, a comment in the adverse events comments field should confirm that the event was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment is an adverse event of special interest and must be reported in an expedited manner (see Section 5.7). The event must be reported as an adverse event with the term of "ejection fraction decreased," as per NCI CTCAE v5.0 (see Appendix 9) and a comment should be added to the adverse events comments field confirming that the event was asymptomatic.

Table 1 summarizes the reporting conventions for LVSD and heart failure.

Table 1 Reporting Conventions for Left Ventricular Systolic Dysfunction / Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of < 10 percentage points from baseline or to an LVEF of ≥ 50%	No additional reporting required; LVEF results to be reported on eCRFs	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline [c] to an LVEF of < 50%	AE [a] (AE eCRF)	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to study treatment discontinuation	AE (AE eCRF) and report as a non-serious AEs of special interest on an SAE eCRF	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD) [b]	AE (AE eCRF) and SAE (SAE eCRF)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE=adverse event; CHF=congestive heart failure; eCRF=electronic case report form; LVEF=left ventricular ejection fraction; LVSD=left ventricular systolic dysfunction; NA=not applicable; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA=New York Heart Association; SAE=serious adverse event.

[a] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[b] Any symptomatic LVSD event must be reported as "heart failure."

[c] Baseline is considered the last LVEF prior to enrolling in study.

G.5.4.3 Administration-Related Reactions: Injection-Related Reactions and Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a specific diagnosis (e.g., "injection-related reaction", "injection-site reaction", "anaphylactic reaction") on the Adverse Event eCRF in the EDC system. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

See Table 2 for the reporting conventions for injection-related reactions and injection-site reactions.

Table 2 Reporting Conventions for Administration-Related Reactions

Adverse Event	Term to Be Used on Adverse Event eCRF Form	Symptoms to Be Entered on eCRF Form
Systemic Injection Reaction	“Injection-related reaction”	Injection reaction
Local Injection Reaction	“Injection-site reaction”	Injection reaction

G.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [A]	(±3)	(±3)	≤28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive ERBB2 gene mutation or amplification by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
ECHO or MUGA [l]	x	As clinically indicated	C1, D15 and every 4 cycles thereafter	x [l]
PH FDC SC administration [m]		x		
Response Assessment [n, o]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [p]		Submit within 21 days of C1, D1		
Whole blood samples [q]	x		see footnote q	
Adverse events [r]	x	Collected on an ongoing basis		*x* [r]
Concomitant Medications [s]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance

imaging; MUGA=multiple-gated acquisition; PD=progressive disease; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ERBB2 gene mutation or amplification status without known TMB-high/MSI-high/dMMR should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] LVEF assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter (e.g. C5D15, C9D15, etc.). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[m] Patients who have had ≥ 6 weeks since their last PH FDC SC (or pertuzumab plus trastuzumab IV) treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations

[n] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[o] At each subsequent tumor assessment, all measurable, and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (± 1) weeks for 3 evaluations, then every 12 (± 2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[p] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[q] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[r] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[s] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study treatment.

Appendix 17
Arm H: PH FDC SC Plus Chemotherapy In Patients With ERBB2 Amplification- or Mutation-Positive Tumors

18. ARM H: PH FDC SC PLUS CHEMOTHERAPY IN PATIENTS WITH ERBB2 AMPLIFICATION OR MUTATION-POSITIVE TUMORS

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H.4 MATERIALS AND METHODS

H.4.1 Patients

To be enrolled in Arm H: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

H.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm H: PH FDC SC plus chemotherapy treatment:

- ERBB2 mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T
  - Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplificationdetermined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy

number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell

- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥ 1500/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (witin 3 months) left ventricular ejection fraction (LVEF) ≥ 50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details regarding contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or 3 months after the last dose of chemotherapy, whichever is later, and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

H.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm H: PH FDC SC plus chemotherapy treatment:

- Diagnosed with breast cancer
- Known tumor mutational burden (TMB) ≥ 10 as determined by a tissue-based NGS assay, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- In addition to the core exclusion criterion for significant cardiovascular disease (see Section 4.1.2), patients will be excluded if they meet any of the following criteria:
  - High-risk arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication
  - Evidence of transmural infarction on ECG

  - Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC
- Current chronic daily treatment with corticosteroids (dose $>$ 10 mg methylprednisolone or equivalent excluding inhaled steroids)

H.4.2 Study Treatment

Study treatment in this arm will consist of PH FDC SC in combination with either docetaxel, paclitaxel, or capecitabine chemotherapy, as determined by the investigator.

H.4.2.1 Formulation and Packaging

PH FDC SC will be provided in two configurations: a loading dose configuration and maintenance dose configuration as single vials:

- Loading dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 20 mL glass colourless vial contains 1200 mg of pertuzumab and 600 mg of trastuzumab in 15 mL of solution.
- Maintenance dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 15 mL colourless glass vial contains 600 mg of pertuzumab and 600 mg of trastuzumab in 10 mL of solution.

For information on the packaging, handling and storage of PH FDC SC, see the Pharmacy Manual and PH FDC SC Investigator's Brochure.

Chemotherapy will consist of either docetaxel, paclitaxel, or capecitabine, as determined by the investigator and will be used in commercially available formulations.

For information on the formulation and handling of docetaxel, paclitaxel, and capecitabine, refer to the respective package insert.

H.4.2.2 Study Treatment Dosage, Administration, and Compliance

Study treatment will be administered in 21 day cycles. PH FDC SC should be administered prior to chemotherapy on days when both are administered.

If a delay in administration of either agent is necessary, reasonable effort should be made to keep the administration synced if clinically feasible (e.g., briefly delay administration of the other agent). A cycle should be considered to start when any drug is administered.

If PH FDC SC is discontinued, chemotherapy can be continued if the patient is likely to derive clinical benefit, as determined by the investigator. If chemotherapy is discontinued, PH FDC SC can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

H.4.2.2.1 PH FDC SC

PH FDC SC is given as a fixed dose (i.e. non-weight based). Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had $\geq$6 weeks since a prior dose of Perjeta and Herceptin intravenous (IV) or PH FDC SC at study entry, or have had $\geq$6 weeks since their last study treatment during the study treatment period, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

All PH FDC SC doses will be administered by SC injection by the investigator or their designee over 5–8 minutes at a rate of $\leq$2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Patients should be monitored for 30 minutes after their first PH FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10–15 minutes following subsequent administrations. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

No dose reductions are allowed for PH FDC SC. If an accidental overdose or medication error occurs, it 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 also be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided Section H.5.2.1.

H.4.2.2.2 Chemotherapy

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

H.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from seven days prior to initiation of study drug until 28 days after the final dose of study treatment. After this period until the end of the study, only medications used for the treatment of cancer will be reported. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

H.4.3.1 Permitted Therapy

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

- H_1-receptor or H_2-receptor antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics, beta blockers, calcium channel blockers, digoxin, thrombocyte aggregation inhibitors
- Analgesics / anti-inflammatories (e.g., paracetamol / acetaminophen, meperidine, opioids)
- Standard therapies for pre-existing medical conditions and medical or surgical complications
- Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) at the investigator's discretion
- Blood transfusions at the investigator's discretion
- Gonadotropin-releasing hormone agonists for fertility preservation
- Vitamin and mineral supplements
- Bone density modifying agents (to be used in accordance with the approved labelled indication and/or nationally recognized treatment guidelines)
- Any other medication not included in the list of prohibited medications

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per institutional 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 institutional 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).

H.4.3.2 Cautionary Therapy

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

H.4.3.3 Prohibited Therapy

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

- Any investigational therapy or agent (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment
- Any targeted anti-cancer treatment other than adjuvant hormone treatment, adjuvant radiotherapy or bone density modifying treatment (e.g. lapatinib, neratinib)
- Regular systemic treatment with steroids

  Short-term corticosteroid to treat and prevent allergic or infusion reactions are allowed however the dose must not exceed $>$20 mg/day of dexamethasone (or equivalent) for $>$7 consecutive days.

- Hormone-replacement therapy
- Use of erythropoiesis-stimulating agents (e.g., erythropoietin)
- Herbal remedies initiated for cancer treatment. Other herbal remedies are discouraged but permitted and must be reported on the appropriate eCRF.
- Topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective estrogen receptor (ER) modulators used with prophylactic intent are prohibited

Postmenopausal women with significant vaginal discomfort associated with anti-estrogen therapy may be considered for intermittent use of low-dose topical estrogens if non-prescription methods are unsuccessful at ameliorating symptoms.

H.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in Arm H: PH FDC SC plus chemotherapy. Refer to the schedule of activities (Section H.6) for arm-specific assessment timepoints.

Cardiac Function

Prior to study enrolment, patients must have an assessment for history of cardiac events, a physical examination, and an LVEF assessment (by ECHO or MUGA) to exclude any cardiac condition that would render them ineligible for participation in this trial. Cardiac function will be assessed locally according to the schedule of activities (see Section H.6).

All patients must have an LVEF ≥50% by ECHO or MUGA scan in order to be eligible for the study. The same LVEF evaluation method should be used throughout the study for each patient and should be performed and assessed by the same assessor if possible. Results of LVEF assessments must be reviewed prior to study treatment administration on the scheduled visit day.

Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and patients in this study require LVEF assessment on more than four occasions within one year.

H.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm H: PH FDC SC plus chemotherapy treatment.

H.5.1 Risks Associated with PH FDC SC plus Chemotherapy

H.5.1.1 Risks Associated with PH FDC SC

PH FDC SC has been associated with risks such as the following: cardiomyopathy, embryo-fetal toxicity, pulmonary toxicity, alopecia, dry skin, rash, nausea, diarrhea, stomatitis, constipation, vomiting, dyspepsia, anemia, neutropenia, fatigue, mucosal inflammation, injection site reaction, pyrexia, dysgeusia, peripheral sensory neuropathy, headache, neuropathy peripheral, paresthesia, dizziness, weight decreased, myalgia, arthralgia, back pain, cough, epistaxis, dyspnea, upper respiratory tract infection, procedural pain, radiation skin injury, decreased appetite, insomnia, and hot flush. Refer to the PH FDC SC Investigator's Brochure for a detailed description of anticipated safety risks for PH FDC SC.

H.5.1.2 Risks Associated with Docetaxel, Paclitaxel, and Capecitabine

Docetaxel has been associated with risks such as the following: infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia.For more details regarding the safety profile of docetaxel, refer to the prescribing information for docetaxel.

Paclitaxel has been associated with risks such as the following: Bone marrow suppression, neutropenia, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Additionally reported adverse events which were less common are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test (LFT) elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis.For more details regarding the safety profile of paclitaxel, refer to the prescribing information for paclitaxel.

Capecitabine has been associated with risks such as the following: diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness and hyperbilirubinemia. For more details regarding the safety profile of capecitabine, refer to the prescribing information for capecitabine.

H.5.2 Management of Patients Who Experience Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

H.5.2.1 Dose Modifications and Interruptions

H.5.2.1.1 Dose Modifications and Interruptions for PH FDC SC

Dose modification of PH FDC SC is not permitted. The administration of PH FDC SC may be delayed to assess or treat adverse events, such as cardiac adverse events.

During the study treatment period, a dose delay of up to (and including) 6 weeks (i.e., up to and including nine weeks between doses) will be permitted to allow adverse event recovery to baseline. Following a dose delay of less than 3 weeks (i.e., $<$6 weeks between doses), study treatment does not need to be reloaded (only the maintenance doses needs to be given).

Patients receiving PH FDC SC with $\geq$6 weeks since their last PH FDC SC treatment or pertuzumab plus trastuzumab IV must receive a loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab FDC SC before continuing with maintenance

doses for subsequent administrations. Patients should be monitored for 30 minutes after their first PH FDC SC dose administration in the study and if a loading dose is required during the study. Patients should be monitored for 10–15 minutes following maintenance dose administrations.

If study treatment is withheld for more than two cycles (>9 weeks) because of toxicity, the patient should be discontinued from study treatment, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor consultation. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Patients who are permanently discontinued from study treatment should be treated at the discretion of the investigator as clinically indicated.

H.5.2.1.2 Dose Modifications and Interruptions for Chemotherapy

Dose modifications and interruptions for docetaxel, paclitaxel, and capecitabine should be done according to standard medical practice and in accordance with the respective packaging insert.

H.5.2.2 Guidelines for Management of Specific Adverse Events Associated with PH FDC SC

Supportive care and medical management of adverse events are at the discretion of the investigator, unless specifically listed below.

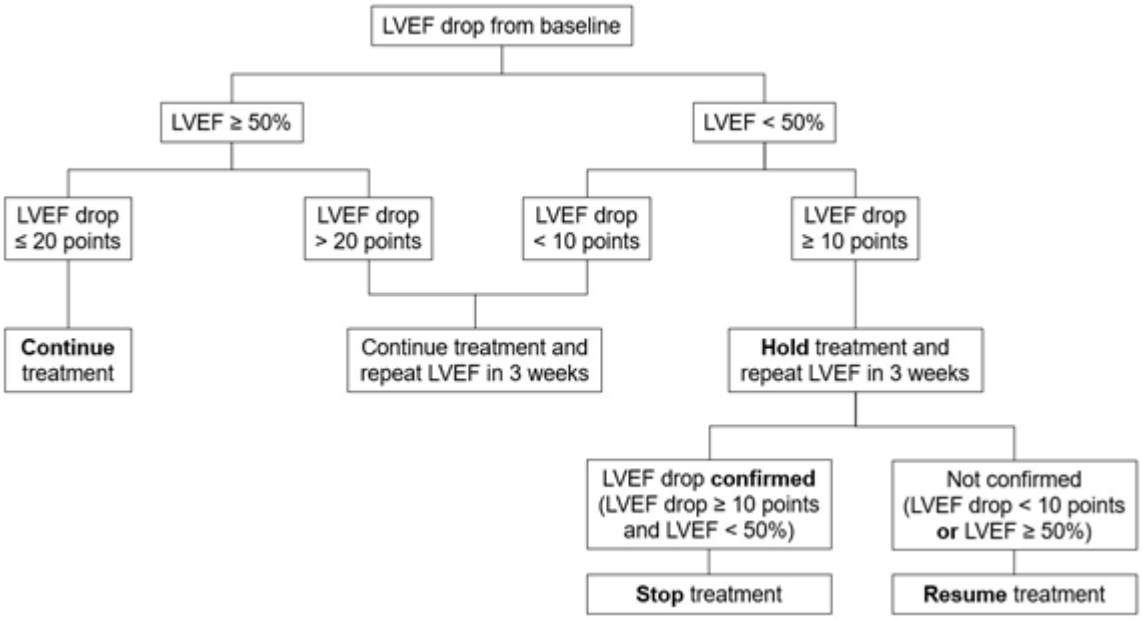
H.5.2.2.1 Symptomatic LVSD and/or LVEF Decline

All patients must have a baseline LVEF ≥50%. LVEF will be monitored regularly according to the Schedule of Activities (Section H.6). If an investigator is concerned that an adverse event may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within 3 weeks. Symptomatic LVSD (CHF) should be assessed as “heart failure” on the basis of NCI CTCAE v5.0 and New York Heart Association (NYHA) classification (see Appendix 9). Symptomatic LVSD (CHF) should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist locally,

Figure 1 summarizes the management of study medication in patients who develop an asymptomatic decrease in LVEF. The decision to initiate study treatment and whether to continue or stop therapy should be based on two factors: measured LVEF and changes in LVEF from baseline. If a significant LVEF decrease occurs, this decrease should be confirmed by a second assessment within approximately 3 weeks showing also a significant decrease.

Heart failure and asymptomatic LVEF decline adverse events must be graded per NCI CTCAE v5.0 (see Appendix 9) and reported in the eCRF as described in Table 2.

Figure 1 Asymptomatic Decline in LVEF: Algorithm for Continuation and Discontinuation of Study Treatment



LVEF=left ventricular ejection fraction.

Patients must have an LVEF ≥50% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) to be eligible for the study.

H.5.2.2.2 Hypersensitivity / Anaphylaxis and Administration-Related Reactions

Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with PH FDC SC, caution should be exercised as these have been associated with Perjeta IV in combination with Herceptin IV and chemotherapy.

Study treatment administration should be stopped in subjects who develop dyspnea or clinically significant hypotension (defined per investigator's discretion).

Patients who experience any of the following events will be discontinued from study treatment:

- Grade 4 allergic reaction

- Grade 3 or 4 hypersensitivity reaction
- Acute respiratory distress syndrome (ARDS)
- Bronchospasm
- Patients who experience administration-related reactions (ARRs) may be managed by:
  - Stopping the injection of PH FDC SC
  - Supportive care with antihistamines, antipyretics, corticosteroids or epinephrine as appropriate at the investigator's discretion, as per institutional practice
  - Subsequently pre-medicating with analgesia and antihistamines as per institutional practice

Patients should be monitored until complete resolution of signs and symptoms of any systemic reactions.

In order to be able to calculate time to onset of such reactions, the occurrence of associated adverse events must be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

All ARRs should be recorded as described in Table 2.

H.5.2.2.3 Diarrhea

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g., loperamide) should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated.

H.5.2.2.4 Rash / Skin Reactions

Treatment recommendations for rash / skin reactions include topical or oral antibiotics, topical pimecrolimus, and topical steroids or systemic steroids (for severe reactions). These agents may be used in patients experiencing pertuzumab-related rash / skin reactions, as clinically indicated, although they have not been studied in this context.

H.5.2.3 Guidelines for Management of Adverse Events Associated with Chemotherapy

Toxicities associated or possibly associated with docetaxel, paclitaxel, or capecitabine treatment should be managed according to standard medical practice and in accordance with the respective packaging insert.

H.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and

Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients in the Arm H: PH FDC SC plus chemotherapy.

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment

H.5.4 Additional Reporting for Selected Adverse Events

Additional data will be collected for the selected adverse events described below.

H.5.4.1 Heart Failure

Symptomatic LVSD (referred to as heart failure) should be reported as a serious adverse event. If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. Heart failure should be graded according to both NCI CTCAE and NYHA Class (see Appendix 9). LVEF fraction results must also be reported.

Heart failure occurring during the study must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

H.5.4.2 Asymptomatic Declines in Left Ventricular Ejection Fraction

Asymptomatic declines in LVEF should not be reported as adverse events because LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows: An asymptomatic decline in LVEF of $\geq$10 percentage-points from baseline to an LVEF $<$50% must be reported as an adverse event with the term of "ejection fraction decreased," as per NCI CTCAE v5.0 (see Appendix 9). In addition, a comment in the adverse events comments field should confirm that the event was asymptomatic.

An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment is an adverse event of special interest and must be reported in an expedited manner (see Section 5.7). The event must be reported as an adverse event with the term of "ejection fraction decreased," as per NCI CTCAE v5.0 (see Appendix 9) and a comment should be added to the adverse events comments field confirming that the event was asymptomatic.

Table 1 summarizes the reporting conventions for LVSD and heart failure.

Table 1 Reporting Conventions for Left Ventricular Systolic Dysfunction / Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of < 10 percentage points from baseline or to an LVEF of ≥ 50%	No additional reporting required; LVEF results to be reported on eCRFs	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline [c] to an LVEF of < 50%	AE [a] (AE eCRF)	Ejection fraction decreased [a]	NCI CTCAE v5.0 for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to study treatment discontinuation	AE (AE eCRF) and report as a non-serious AEs of special interest on an SAE eCRF	Ejection fraction decreased [a]	NCI CTCAE v5.0 for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD) [b]	AE (AE eCRF) and SAE (SAE eCRF)	"Heart failure"	NCI CTCAE v5.0 for "heart failure" and NYHA class

AE=adverse event; CHF=congestive heart failure; eCRF=electronic case report form; LVEF=left ventricular ejection fraction; LVSD=left ventricular systolic dysfunction; NA=not applicable; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; NYHA=New York Heart Association; SAE=serious adverse event.

[a] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[b] Any symptomatic LVSD event must be reported as "heart failure."

[c] Baseline is considered the last LVEF prior to enrolling in study.

H.5.4.3 Administration-Related Reactions: Injection-Related Reactions and Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a specific diagnosis (e.g., "injection-related reaction," "injection-site reaction", "anaphylactic reaction") on the Adverse Event eCRF in the EDC system. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

See Table 2 for the reporting conventions for injection-related reactions and injection-site reactions.

Table 2 Reporting Conventions for Administration-Related Reactions

Adverse Event	Term to Be Used on Adverse Event eCRF Form	Symptoms to Be Entered on eCRF Form
Systemic Injection Reaction	“Injection-related reaction”	Injection reaction
Local Injection Reaction	“Injection-site reaction”	Injection reaction

H.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [A]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive ERBB2 gene mutation or amplification by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
ECHO or MUGA [m]	x	As clinically indicated	C1, D15 and every 4 cycles thereafter	x
PH FDC SC administration [n]		x		
Chemotherapy administration [o]		x		
Response Assessment [p, q]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [r]		Submit within 21 days of C1, D1		
Whole blood samples [s]	x		see footnote s	
Adverse events [t]	x	Collected on an ongoing basis		*x* [t]
Concomitant Medications [u]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; PH FDC SC= fixed dose combination of pertuzumab trastuzumab administered subcutaneously; PET=positron emission tomography; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ERBB2 gene mutation or amplification status without known TMB-high/MSI-high/dMMR should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a

serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] LVEF assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter (e.g. C5D15, C9D15, etc.). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[n] Patients who have had ≥ 6 weeks since their last PH FDC SC or pertuzumab plus trastuzumab IV treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations

[o] Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

[p] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[q] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[r] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[s] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[t] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[u] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study treatment.

Appendix 18
Arm I: Trastuzumab Emtansine plus Tucatinib in Patients with ERBB2 Amplification- or Mutation-Positive Tumors

19. ARM I: TRASTUZUMAB EMTANSINE PLUS TUCATINIB IN PATIENTS WITH ERBB2 AMPLIFICATION- OR MUTATION-POSITIVE TUMORS

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I.4 MATERIALS AND METHODS

I.4.1 Patients

To be enrolled in Arm I: trastuzumab emtansine plus tucatinib treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

I.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- ERBB2 mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T
  - Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- ANC $\geq 1200/\mu l$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last administration of tucatinib, whichever is longer; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details regarding requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a

failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last dose of tucatinib, whichever is longer, and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

I.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10 as determined by a tissue-based NGS assay, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin > 500 mg/m^2
  - Liposomal doxorubicin > 500 mg/m^2
  - Epirubicin > 720 mg/m^2
  - Mitoxantrone > 120 mg/m^2
  - Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of severe hypersensitivity to components of the trastuzumab emtansine or tucatinib formulations
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - Inadequate left ventricular ejection fraction at baseline, < 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  - History of decrease in left ventricular ejection function to < 40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade ≥ 2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia

  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Have used a strong cytochrome P450 (CYP)2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 day prior to start of treatment
- Grade $\geq$3 peripheral neuropathy, as defined by CTCAE v5.0
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia

I.4.2 Study Treatment

Study treatment in this arm will consist of trastuzumab emtansine in combination with tucatinib.

I.4.2.1 Formulation and Packaging

Trastuzumab emtansine is provided as a lyophilized product in either 15-mL or 20-mL single-use vials which contain enough product to deliver 100 mg or 160 mg, respectively, of trastuzumab emtansine. The lyophilized form of the product is provided for reconstitution to a liquid concentrate using sterile water for injection. After reconstitution, both the 15-mL and 20-mL vials contain 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 6% w/v sucrose, and 0.02% (w/v) polysorbate 20. The reconstituted product contains no preservative and is intended for single use only. The density of the drug product after reconstitution is 1.026 g/mL.

For information on the formulation and handling of trastuzumab emtansine, see the pharmacy manual and the Trastuzumab Emtansine Investigator's Brochure.

Tucatinib drug product may be supplied as both a coated oval-shaped tablet in a 150 mg dosage strength and a coated round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

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

I.4.2.2 Dosage, Administration, and Compliance

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient’s baseline weight. Weight will be measured at

each visit and dose must be re-adjusted for weight changes > 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. The calculated total dose may be rounded to the nearest milligram.

Trastuzumab emtansine should be administered as described in Table 1. The initial dose will be administered over 90 minutes. Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed predose and postdose. Following the initial dose, patients will be observed for at least 90 minutes. Subsequent doses of trastuzumab emtansine may be administered over 30 minutes.

Table 1 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • Administer the initial dose as a 90-minute intravenous infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions • Patient should be observed during the infusions and for at least 30 minutes after infusion.

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

Tucatinib 300 mg will be administered PO BID continuously starting from Cycle 1 Day 1 onwards. Tucatinib should be taken once in the morning and once in the evening, with approximately 8 to 12 hours between doses in the same calendar day.

It is recommended that if a subject misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose.

Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed, cut or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Guidelines for trastuzumab emtansine dosage modification and treatment interruption or discontinuation are provided in Section I.5.2.1.1

Guidelines for tucatinib dosage modification and treatment interruption or discontinuation are provided in Section I.5.2.1.2

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

I.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

I.4.3.1 Permitted Therapy

Use of the following therapies is permitted during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Erythropoiesis-stimulating agents or granulocyte colony-stimulating factors

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

I.4.3.2 Prohibited Therapy

Use of the following therapy is prohibited during study treatment:

- Any systemic therapy intended for the treatment of the disease under study, including any other investigational agent
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib. Concomitant use of potent CYP P450 3A4/5 inhibitors (such as ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. Consider an alternate medication with

no or minimal potential to inhibit CYP3A4/5. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.

- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment; Strong inhibitors of CYP2C8 are also prohibited within 1 week of discontinuation of tucatinib (see Appendix 7). Moderate inhibitors of CYP2C8 should be used with caution.
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (see Appendix 7). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.
- Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.
- 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 and during study treatment (See Section 4.1.2), until disease progression is documented and the patient has discontinued study treatment.
  - Palliative radiation therapy for the treatment of bone pain for bone metastases in the absence of progressive disease is permitted, however tucatinib should be held during and for 7 days following radiation therapy.

I.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients receiving trastuzumab emtansine plus tucatinib. Refer to the schedule of activities (Section I.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation: INR and aPTT
- Liver function test: ALT/AST, total bilirubin

Functional Assessments

- ECHO/MUGA

I.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm I: trastuzumab emtansine plus tucatinib treatment.

I.5.1 Risks Associated with Trastuzumab Emtansine plus Tucatinib

I.5.1.1 Risks Associated with Trastuzumab Emtansine

Trastuzumab emtansine has been associated with risks such as the following: hepatotoxicity, (predominantly in the form of asymptomatic increases in the concentrations of serum transaminases; serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver), left ventricular dysfunction, infusion-related reaction (IRR), hypersensitivity, hemorrhagic events, (including CNS, respiratory, and gastrointestinal hemorrhage), thrombocytopenia, peripheral neuropathy, reactions secondary to extravasation, interstitial lung disease (including pneumonitis). Refer to the Trastuzumab Emtansine Investigator's Brochure for a description of all anticipated safety risks for trastuzumab emtansine.

I.5.1.2 Risks Associated with Tucatinib

Tucatinib has been associated with risks such as the following: diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, rash, arthralgia, creatinine increased, weight decreased, peripheral neuropathy, and epistaxis. Refer to the Tucatinib USPI for a detailed description of anticipated safety risks for tucatinib. Guidelines for Management of Adverse Events.

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

I.5.2 Management of Patients Who Experience Adverse Events

I.5.2.1 Dose Modications and Interruptions

I.5.2.1.1 Dose Modifications and Interruptions for Trastuzumab Emtansine

For adverse events not listed below in Section I.5.2.2 the following guidance should be used with regards to dose delays and modifications:

- For Grade 3 non-hematologic adverse events not adequately managed by standard medical intervention or for any Grade 4 non-hematologic adverse event, study treatment should be held until recovery to Grade ≤ 1. A maximum dose delay of 42 days for the last administered dose of study drug will be allowed.

- If withheld for <42 days, trastuzumab emtansine may be resumed at either the same dose level as before or at one dose level lower (see Table 2), at the discretion of the investigator. Subsequent cycles should remain every 21 days.
- Dose re-escalation is not permitted for trastuzumab emtasine.
- Resuming trastuzumab emtanzine after 42 days may be considered in exceptional circumstances and should be done in consultation with the Medical Monitor.

Table 2 Recommended Dose Reduction Schedule for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Permanently discontinue

I.5.2.1.2 Dose Modifications and Interruptions for Tucatinib

Up to three dose reductions of tucatinib are allowed. Dose reductions of larger intervals than those described in Table 3. Dose re-escalation is not permitted for tucatinib.

Table 3 Tucatinib: Recommended Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	Tucatinib Dose Level
Starting dose	300 mg PO BID [a]
1st dose reduction	250 mg PO BID
2nd dose reduction	200 mg PO BID
3rd dose reduction	150 mg PO BID
Requirement for further dose reduction	Discontinue tucatinib

[a] Dose reductions of greater intervals than those recommended in this table (i.e., more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator in consultation with the Medical Monitor. However, tucatinib may not be dose reduced below 150 mg BID.

I.5.2.2 Guidelines for Management of Specific Adverse Events for Trastuzumab Emtansine

I.5.2.2.1 Cardiotoxicity

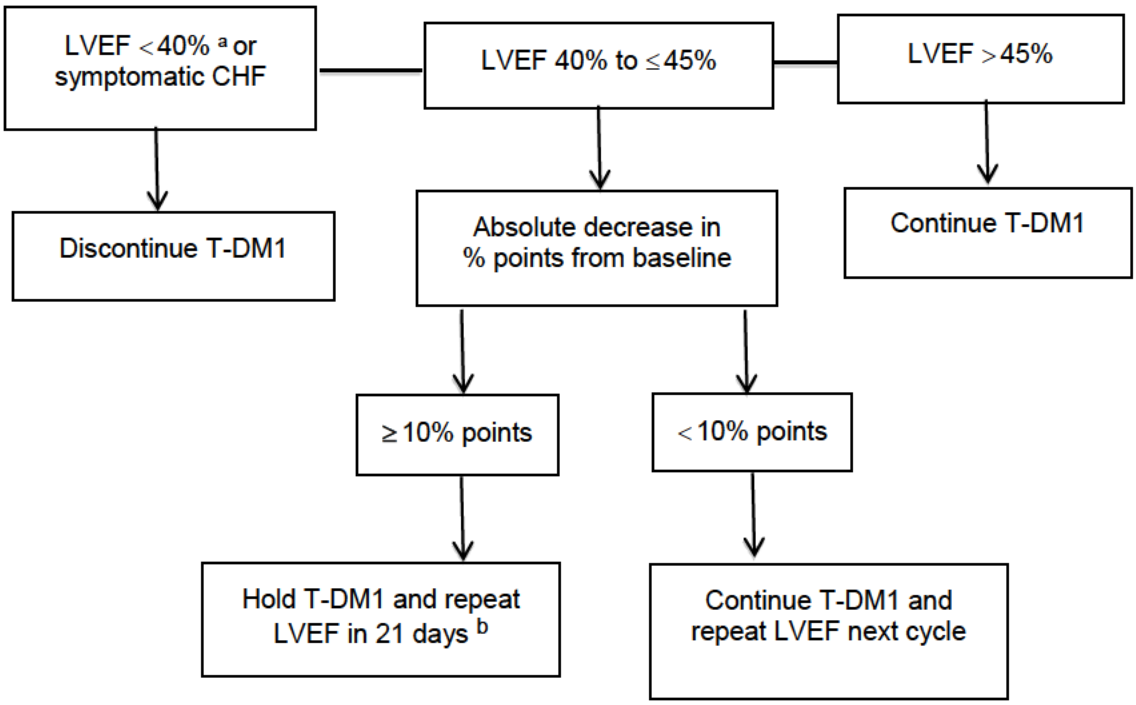
Patients without significant cardiac history and with a baseline LVEF of >50% as determined by ECHO or MUGA scan are eligible for arm participation. Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in this arm.

Assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed (Section I.6).

Figure 1 summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in patients. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 1 or asymptomatic declines in LVEF. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed decrease of LVEF to $<40\%$ is documented (with a confirmation assessment carried out within 21 days). For patients whose LVEF decreases to values of 40%–45% with an absolute decrease in LVEF of $\geq 10\%$ points from baseline, trastuzumab emtansine dose should be held. For these patients, the LVEF measurement should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if the LVEF has not recovered to within a 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain LVEF, the patient should be discontinued from all study treatment.

Figure 1 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Patients



CHF=congestive heart failure; LVEF=left ventricular ejection fraction; T-DM1=trastuzumab emtansine.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] LVEF <40% should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if LVEF <40% is confirmed. Trastuzumab emtansine should be held while the confirmatory LVEF measurement is obtained.

[b] After a second consecutive confirmatory measurement is obtained, trastuzumab emtansine treatment should be discontinued if the ≥10% absolute LVEF decrease from baseline is confirmed.

I.5.2.2.2 Infusion-Related Reactions and Hypersensitivity Reactions

See Table 4 for management guidelines for trastuzumab emtansine-associated infusion-related reactions and hypersensitivity reactions.

Table 4 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.

I.5.2.2.3 Hematologic Toxicities

See Table 5 for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 5 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade 2 thrombocytopenia (50,000 to 75,0000/μL)	Assess platelet counts weekly or as medically indicated until recovery. Withhold study treatment until Grade ≤ 1. Resume treatment without dose reduction.
Grade 3 thrombocytopenia (25,000 to < 50,000/μL)	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/μL) at any time	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade ≥ 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

I.5.2.2.4 Neuropathy

See Table 6 for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 6 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade ≥ 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

I.5.2.2.5 Hepatotoxicity

Dose modification guidelines for trastuzumab emtansine and elevated liver function tests are provided in Table 7 and Table 8. For dose modifications for tucatinib, see Section I.5.2.3.

Trastuzumab emtansine must be permanently discontinued in patients with either Grade 4 transaminase elevations or Grade 4 total bilirubin elevations.

Dose reductions are recommended for Grade 3 hepatic events (e.g., liver dysfunction, elevated AST, ALT, and/or total bilirubin). The dose should be held in accordance with the dose delay guidance described in Table 7. Dosage Modification for Toxicity to allow for recovery to Grade ≤ 2 (transaminase levels) and/or Grade ≤ 1 (total bilirubin level) prior to resuming trastuzumab emtansine at a lower dose level. Patients who experience a Grade 2 total bilirubin elevation should have the dose held to allow for recovery to Grade ≤ 1 prior to resuming trastuzumab emtansine. Patients who experience a Grade 3 hepatic event at the lowest dose level will be discontinued from study treatment. No reescalation of the trastuzumab emtansine dose will be allowed.

Patients with ALT and/or AST $> 3 \times$ the ULN concurrent with total bilirubin $> 2 \times$ ULN and/or clinical jaundice should discontinue trastuzumab emtansine.

Trastuzumab emtansine must be permanently discontinued in patients who are diagnosed with NRH.

Patients with increased total bilirubin because of Gilbert syndrome are allowed to continue trastuzumab emtansine dosing without a dose hold or dose modification if the direct (conjugated) bilirubin level is within the normal reference range.

Table 7 Dose Modification Guidelines for Hypertransaminasemia (AST/ALT)

	Grade 4 (> 20 × the ULN *if baseline was normal; > 20.0 × baseline if baseline was abnormal*)	**Grade 3** (> 5 to 20× the ULN *if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal)*	**Grade 2** (> *3.0* to 5.*0* × the ULN *if baseline was normal; > 3.0–5.0 × baseline if baseline was abnormal*)
Trastuzumab emtansine	Discontinue	Hold dose; reduce one dose level when recovered to Grade ≤ 2. Discontinue if concurrent with a bilirubin > 2 × the ULN or clinical jaundice.	Treat at the same dose level. Discontinue if concurrent [a] with a bilirubin > 2 × the ULN or clinical jaundice.

ALT=alanine transaminase; AST=aspartate transaminase; ULN=upper limit of normal.
Note: A maximum of two dose reductions of trastuzumab emtansine is allowed. A patient requiring more than two dose reductions must discontinue study treatment.

[a] Within 21 days.

Table 8 Dose Modification Guidelines for Hyperbilirubinemia

	Grade 4 (> 10.*0* × the ULN *if baseline was normal; > 10.0 × baseline if baseline was abnormal*)	**Grade 3** (> 3.*0* to 10.*0* × the ULN *if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal*)	**Grade 2** (> 1.5 to 3.*0* × the ULN *if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal*)	**Grade 1** (*> ULN–1.5 × ULN if baseline was normal; 1.0–1.5 × baseline if baseline was abnormal*)
Trastuzumab emtansine	Discontinue	Hold dose; reduce one dose level when recovered to Grade ≤ 1 or baseline. Discontinue if concurrent [a] with ALT or AST > 3 × the ULN.	Hold dose; treat at same dose level when recovered to Grade ≤ 1. Discontinue if > 2 × the ULN and concurrent [a] with ALT or AST > 3 × the ULN.	Treat at same dose level.

ALT=alanine transaminase; AST=aspartate transaminase; ULN=upper limit of normal.
Note: A maximum of two dose reductions of trastuzumab emtansine is allowed. A patient requiring more than two dose reductions must discontinue study treatment.

[a] Within 21 days.

I.5.2.2.6 Pulmonary Toxicity

It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis due to trastuzumab emtansine.

I.5.2.3 Guidelines for Management of Specific Adverse Events for Tucatinib

General dose modification guidelines for clinical adverse events related tucatinib are provided Table 9 and Table 10. For subjects with documented Gilbert's disease, contact the medical monitor for guidance regarding dose modifications for LFT abnormalities. For dose modifications for trastuzumab emtansine, see Section I.5.2.2.

Table 9 Dose Modifications for Clinical Adverse Events Related to Tucatinib

Adverse Reactions	Tucatinib Dose Modification
Diarrhea	
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to Grade ≤ 1 or baseline Resume tucatinib at same dose level
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to Grade ≤ 1 or baseline Reduce tucatinib dose.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue tucatinib treatment.
Other adverse reactions	
Grade 3	Hold tucatinib until recovery to Grade ≤ 1 or baseline Reduce tucatinib dose
Grade 4	Permanently discontinue tucatinib.

Table 10 Dose Modifications of Tucatinib for LFT Abnormalities, Regardless of Relationship to Tucatinib

Laboratory Abnormality	Tucatinib Dose Modification
Grade 2 Bilirubin elevation > 1.5–3 × ULN *if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal*	Hold tucatinib until recovery to ≤ 1.5 × ULN Resume tucatinib at same dose level
Grade 3 Bilirubin elevation > 3–10 × ULN *if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal*	Hold tucatinib until recovery to ≤ 1.5 × ULN Reduce tucatinib dose.
Grade 4 Bilirubin elevation > 10 × ULN *if baseline was normal; > 10.0 × baseline if baseline was abnormal*	Permanently discontinue tucatinib.
Grade 3 ALT or AST elevation > 5–20 × ULN *if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal*	Hold tucatinib until recovery to ≤ 3 × ULN or return to baseline level in subjects with known liver metastasis Reduce tucatinib dose.
Grade 4 ALT or AST elevation > 20 × ULN *if baseline was normal; > 20.0 × baseline if baseline was abnormal*	Permanently discontinue tucatinib.
ALT or AST > 3 × ULN *if baseline was normal; > 3 × baseline if baseline was abnormal* AND bilirubin > 2 × ULN *if baseline was normal; > 2 × baseline if baseline was abnormal*	Permanently discontinue tucatinib.

I.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately:

Tucatinib

Hepatotoxicity

- AST or ALT elevations that are >3 x ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2 x ULN, except in subjects with documented Gilbert's syndrome

- Grade 4 AST, ALT, or bilirubin elevations

Measurement of direct and indirect bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. The sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Trastuzumab Emtansine

- N/A

I.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 to −1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive ERBB2 gene mutation or amplification by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status i[i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation Panel [m]	x			x
Liver function test [n]			C1, D15 and C2, D15	
ECHO or MUGA [o]	x	As clinically indicated	C1, D15 and every 4 cycles thereafter	x [o]
Trastuzumab emtansine administration [p]		x		
Tucatinib compliance assessment [q]		x		x
Tucatinib dispensing		x		

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 to −1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Response Assessment [r, s]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [t]		Submit within 21 days of C1, D1		
Whole blood samples [u]	x		see footnote u	
Adverse events [v]	x	Collected on an ongoing basis		*x* [v]
Concomitant Medications [w]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; PET=positron emission tomography; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ERBB2 gene mutation or amplification status without known TMB-high/MSI-high/dMMR should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes INR and aPTT.

[n] Liver function test includes ALT/AST, total bilirubin.

[o] LVEF assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter (e.g. C5D15, C9D15, etc.). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[p] Trastuzumab emtansine will be administered by IV infusion at a dose of 3.6 mg/kg on Day 1 of Cycle 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-

related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[q] Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.

[r] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[s] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[t] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[u] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study treatment.

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Appendix 19
Arm J: Trastuzumab Emtansine Plus Atezolizumab in Patients with ERBB2 Amplification Or Mutation Plus TMB-H/MSI-H/dMMR-Positive Tumors

20. ARM J: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH ERBB2 AMPLIFICATION OR MUTATION PLUS TMB-H/MSI-H/DMMR-POSITIVE TUMORS

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J.4 MATERIALS AND METHODS

J.4.1 Patients

To be enrolled in Arm J: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

J.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- ERBB2 mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  - Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S
  - Kinase domain: T733I; L755P/S; L755_T759del; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C
  - Transmembrane domain: S653C; V659E; G660D; R678Q
  - GFR domain IV: P551L; R552S
  - Receptor L: S418T; A440T
  - Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell

- Documentation of one of the following biomarkers, as determined by a CLIA or equivalently certified assay (tissue or blood):
  - Tumor mutational burden (TMB) high, defined as ≥ 10 mutations per megabase as determined by a tissue-based NGS assay
  - Microsatellite instability high (MSI-H)

  - Deficient mismatch repair (dMMR)
- ANC ≥ 1200/μl within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizumab, whichever is longer; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details regarding requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period. See Appendix 2 for details regarding contraception requirements.

J.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer
- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin >500 mg/m^2
  - Liposomal doxorubicin >500 mg/m^2
  - Epirubicin >720 mg/m^2
  - Mitoxantrone >120 mg/m^2
  - Idarubicin >90 mg/m^2

    If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - Uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg)
  - Inadequate left ventricular ejection fraction at baseline, <50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)

  - History of symptomatic congestive heart failure Grade ≥3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) or Class ≥II New York Heart Association
  - History of decrease in left ventricular ejection function to <40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of enrollment
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade ≥2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  - Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium >upper limit of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade ≥ 3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  - 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

- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain

  Patients requiring 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 ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation.

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

- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (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−TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

J.4.2 Study Treatment

Study treatment in this arm will consist of atezolizumab in combination with trastuzumab emtansine.

J.4.2.1 Formulation and Packaging

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.

Trastuzumab emtansine is provided as a lyophilized product in either 15-mL or 20-mL single-use vials which contain enough product to deliver 100 mg or 160 mg, respectively, of trastuzumab emtansine. The lyophilized form of the product is provided for reconstitution to a liquid concentrate using sterile water for injection. After reconstitution, both the 15-mL and 20-mL vials contain 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 6% w/v sucrose, and 0.02% (w/v) polysorbate 20. The reconstituted product contains no preservative and is intended for single use only. The density of the drug product after reconstitution is 1.026 g/mL.

For information on the formulation and handling of trastuzumab emtansine, see the pharmacy manual and the Trastuzumab Emtansine Investigator's Brochure.

J.4.2.2 Dosage, Administration, and Compliance

Atezolizumab will be administered first followed by trastuzumab emtansine.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a]. • 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. [a] • 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 measured within 60 minutes prior to the infusion [a]. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained as directed but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section E.5.2.2.6.

No dose modification for atezolizumab is allowed.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity (or loss of clinical benefit with Medical Monitor consultation when given in combination with atezolizumab; see Section 3.1.2 for treatment beyond disease progression). The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes $>$ 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. The calculated total dose may be rounded to the nearest milligram.

The initial dose will be administered over 90 minutes. Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed predose and postdose. Following the initial dose, patients will be observed for at least 90 minutes. Subsequent doses of trastuzumab emtansine may be administered over 30 minutes. Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section J.5.2.2.4.

If a delay in administration of either agent is necessary, reasonable effort should be made to keep the administration synced if clinically feasible (e.g., briefly delay administration of the other agent). A cycle should be considered to start when any drug is administered.

Table 2 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • Administer the initial dose as a 90-minute intravenous infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured [a] • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions • Patient should be observed during the infusions and for at least 30 minutes after infusion.

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

J.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

J.4.3.1 Permitted Therapy

Use of the following therapies is permitted during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section J.4.3.2)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma

- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for the prevention or delay of skeletal complications, and palliation of bone pain in patients with documented bone metastases. Use bisphosphonates or other agents for hypercalcemia or malignancy is prohibited and patients requiring such treatment should be evaluated for progressive disease.
- Erythropoiesis-stimulating agents or granulocyte colony-stimulating factors
- Radiation therapy for the treatment of bone pain for bone metastases in the absence of progressive disease
- Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, as clinically indicated.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

J.4.3.2 Prohibited Therapy

Use of the following therapy is prohibited during study treatment:

- Any systemic therapy intended for the treatment of the disease under study, including any other investigational agent
- Concomitant use of potent cytochrome (CYP) P450 3A4/5 inhibitors (such as ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4/5. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.
- Any hormonal therapy used for the treatment of the disease under study. Patients who require the use of these agents will be discontinued from study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these

agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited within 2 weeks prior to the initiation of study treatment and during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed.

J.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients receiving trastuzumab emtansine plus atezolizumab. Refer to the schedule of activities (Section J.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation: INR and aPTT
- Thyroid function test (thyroid-stimulating hormone [TSH], free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)

Functional Assessments

- ECHO/MUGA

J.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm J: trastuzumab emtansine plus atezolizumab treatment.

J.5.1 Risks Associated with Trastuzumab Emtansine plus Atezolizumab

J.5.1.1 Risks Associated with Trastuzumab Emtansine

Trastuzumab emtansine has been associated with risks such as the following: interstitial lung disease, (including pneumonitis), hepatotoxicity, (predominantly in the form of asymptomatic increases in the concentrations of serum transaminases; serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver), left ventricular dysfunction, IRR, hypersensitivity, hemorrhagic events, (including CNS, respiratory, and gastrointestinal hemorrhage), thrombocytopenia, peripheral neuropathy, and reactions secondary to extravasation. Refer to the Trastuzumab Emtansine Investigator's Brochure for a description of all anticipated safety risks for trastuzumab emtansine.

J.5.1.2 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 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Suggested workup and management guidelines for overlapping toxicities between atezolizumab and trastuzumab emtansine, pulmonary and hepatic events, are provided in Section J.5.2.4.

J.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

J.5.2.1 Dose Modifications and Interruptions

J.5.2.1.1 Dose Modifications and Interruptions for Trastuzumab Emtansine

For adverse events not listed below in Section J.5.2.2 the following guidance should be used with regards to dose delays and modifications:

- For Grade 3 non-hematologic adverse events not adequately managed by standard medical intervention or for any Grade 4 non-hematologic adverse event, study treatment should be held until recovery to Grade ≤ 1. A maximum dose delay of 42 days for the last administered dose of study drug will be allowed.
- If withheld for <42 days, trastuzumab emtansine may be resumed at either the same dose level as before or at one dose level lower (see Table 3), at the discretion of the investigator. Subsequent cycles should remain every 21 days.
- Dose re-escalation is not permitted for trastuzumab emtasine.
- Resuming trastuzumab emtanzine after 42 days may be considered in exceptional circumstances and should be done in consultation with the Medical Monitor.

Table 3 Recommended Dose Reduction Schedule for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Permanently discontinue

J.5.2.1.2 Dose Modifications and Interruptions for Atezolizumab

No dose reductions for atezolizumab are allowed. Interruptions to atezolizumab treatment are described in Section E.5.2.1.1.

J.5.2.2 Guidelines for Management of Specific Adverse Events for Trastuzumab Emtansine

J.5.2.2.1 Hepatotoxicity

Hepatotoxicity is an overlapping toxicity for trastuzumab emtansine and atezolizumab. Management guidelines are provided in Section J.5.2.4.2.

J.5.2.2.2 Pulmonary Toxicity

Pulmonary Toxicity is an overlapping toxicity for trastuzumab emtansine and atezolizumab. Management guidelines are provided in Section J.5.2.4.1

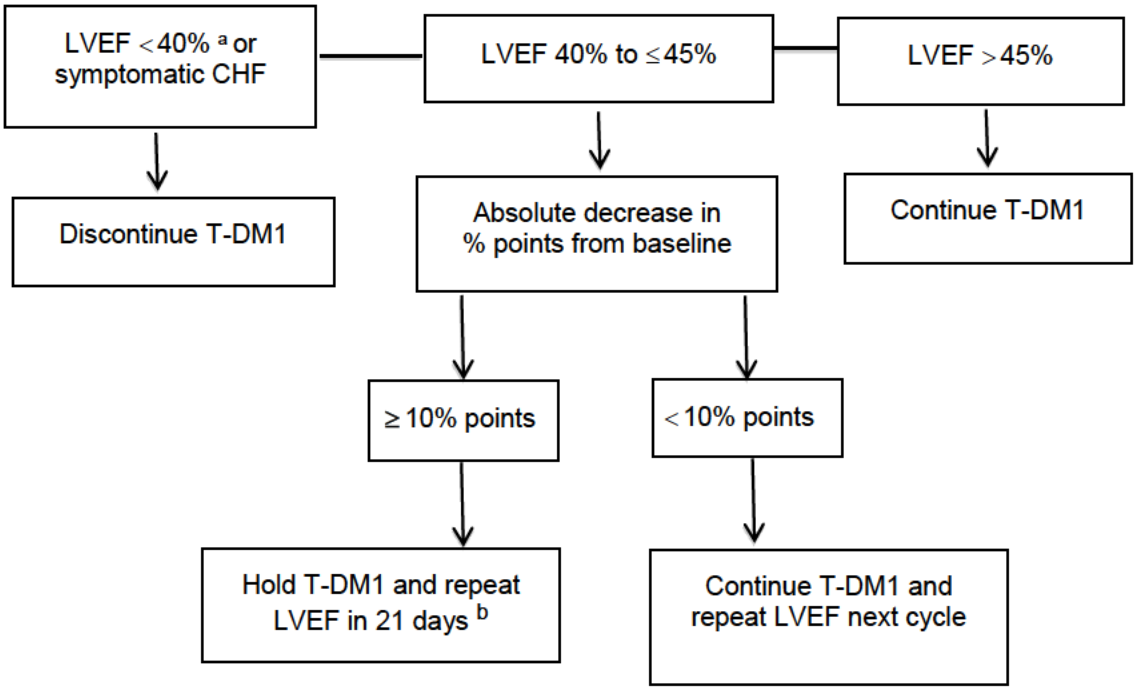
J.5.2.2.3 Cardiotoxicity

Patients without significant cardiac history and with a baseline LVEF of ≥ 50% as determined by ECHO or MUGA scan are eligible for arm participation. Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in this arm. Assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed > 28 days before last study treatment administration and if no post-treatment evaluation was performed (see Section J.6).

Figure 1 summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in patients. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 1 or asymptomatic declines in LVEF. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed decrease of LVEF to < 40% is documented (with a confirmation assessment carried out within 21 days). For patients whose LVEF decreases to values of 40%–45% with an absolute decrease in LVEF of ≥ 10% points from baseline, trastuzumab emtansine dose should be held. For these patients, the LVEF measurement should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if the LVEF has not recovered to within a 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain LVEF, the patient should be discontinued from all study treatment.

Figure 1 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Patients



CHF=congestive heart failure; LVEF=left ventricular ejection fraction; T-DM1=trastuzumab emtansine.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] LVEF <40% should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if LVEF <40% is confirmed. Trastuzumab emtansine should be held while the confirmatory LVEF measurement is obtained.

[b] After a second consecutive confirmatory measurement is obtained, trastuzumab emtansine treatment should be discontinued if the ≥10% absolute LVEF decrease from baseline is confirmed.

J.5.2.2.4 Infusion-Related Reactions and Hypersensitivity Reactions

See Table 4 for management guidelines for trastuzumab emtansine-associated infusion-related reactions and hypersensitivity reactions.

Table 4 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.

J.5.2.2.5 Hematologic Toxicities

See Table 5 for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 5 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade 2 thrombocytopenia (50,000 to 75,0000/μL)	Assess platelet counts weekly or as medically indicated until recovery. Withhold study treatment until Grade ≤ 1. Resume treatment without dose reduction.
Grade 3 thrombocytopenia (25,000 to < 50,000/μL)	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/μL) at any time	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade ≥ 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

J.5.2.2.6 Neuropathy

See Table 6 for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 6 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade ≥ 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

J.5.2.3 Guidelines for Management of Adverse Events Associated with Atezolizumab

Guidelines for management of adverse events associated with atezolizumab can be found in Section E.5.2.2

J.5.2.4 Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

The following adverse events are potential overlapping toxicities associated with combination use of trastuzumab emtansine and atezolizumab: pulmonary and hepatic events.

J.5.2.4.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates.

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:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study, and will also have CT scans of the chest at every tumor assessment. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* See Table 7 for management guidelines for pulmonary events and pneumonitis.

In this study, atezolizumab and trastuzumab emtansine are discontinued for all grades of interstitial lung disease and pneumonitis.

Table 7 Management Guidelines for Interstitial Lung Disease and Pneumonitis

Severity	Trastuzumab Emtansine	Atezolizumab
Grade 1 – 4	Discontinue trastuzumab emtansine treatment.	Discontinue atezolizumab treatment

J.5.2.4.2 Hepatic Events

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Liver function will be monitored throughout study treatment.

While on this study, patients who present 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.

If outcome of LFTs is worsening, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for worsening outcome of LFTs. Antinuclear antibody, perinuclear antineutrophil cytoplasmic antibody, antiliver kidney microsomal antibodies, and antismooth muscle antibody tests should be performed if an autoimmune etiology is considered. See Table 8 for management guidelines for atezolizumab and trastuzumab emtansine hepatic events.

See Table 8 for Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events. See Table 9 for dose modifications of trastuzumab emtansine for hyperbilirubinemia.

Note: No dose modification for atezolizumab is indicated on the basis of hyperbilirubinemia alone.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Atezolizumab	Trastuzumab Emtansine
ALT or AST increase that meets Hy's law criteria: ALT or AST $>3\times$ ULN, in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue atezolizumab treatment.	Discontinue trastuzumab emtansine treatment.
Grade 1 *AST or ALT > ULN–3.0 × ULN if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal*	Treat at the same dose level. Continue LFT monitoring.	Treat at the same dose level.
Grade 2 *AST or ALT >3.0–5.0 × ULN if baseline was normal; >3.0–5.0 × baseline if baseline was abnormal*	Withhold atezolizumab dose. If persists >5–7 days: Consider starting 1–2 mg/kg/day prednisone or equivalent per day; when recover to Grade ≤ 1, taper steroids over ≥ 1 month. Resume therapy when systemic steroid dose is $\leq$ 10mg oral prednisone equivalent per day and resume when recovery to Grade ≤ 1 at same dose within 12 weeks. Permanently discontinue atezolizumab and contact the Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.	Treat at the same dose level.

GI=gastrointestinal; LFT=liver function test; NRH=Nodular Regenerative Hyperplasia; TNF=tumor necrosis factor; ULN=upper limit of normal.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab	Trastuzumab Emtansine
Grade 3 *AST or ALT > 5.0–20.0 × ULN if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal*	Discontinue atezolizumab dose. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab treatment is discontinued.	Withhold trastuzumab emtansine dose. Do not administer trastuzumab emtansine until recovery to Grade ≤ 2, and then resume with dose reduction by one level. Discontinue trastuzumab emtansine treatment if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.
Grade 4 *AST or ALT > 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal*	Discontinue atezolizumab treatment. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab treatment is discontinued.	Discontinue trastuzumab emtansine treatment. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.

GI=gastrointestinal; LFT=liver function test; NRH=Nodular Regenerative Hyperplasia; TNF=tumor necrosis factor; ULN=upper limit of normal.

Table 8 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab	Trastuzumab Emtansine
NRH If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered.	Discontinue atezolizumab treatment	Discontinue trastuzumab emtansine treatment and have the patient evaluated by a hepatologist.

GI=gastrointestinal; LFT=liver function test; NRH=Nodular Regenerative Hyperplasia; TNF=tumor necrosis factor; ULN=upper limit of normal.

Table 9 Trastuzumab Emtansine Dose Modification Guidelines for Hyperbilirubinemia

Severity	Action to be Taken
Grade 2 *Total bilirubin > 1.5–3.0 × ULN if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal*	Withhold until total bilirubin recovers to Grade ≤1 and then resume at the same dose level.
Grade 3 *Total bilirubin > 3.0 - 10.0 × ULN if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal*	Withhold until total bilirubin recovers to Grade ≤1 and then resume by one dose level reduction.
Grade 4 *Total bilirubin > 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal*	Discontinue trastuzumab emtansine treatment.

ULN = upper limit of normal.

J.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special

interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately:

Atezolizumab

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

Trastuzumab Emtansine

- Not Applicable

J.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [A]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive ERBB2 gene mutation or amplification plus TMB-H/MSI-H/dMMR by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation Panel [m]	x			x
Thyroid function test (TSH, free T3 [or total], and free T4) [n]	x	C1, D1 and every 4 cycles thereafter		
ECHO or MUGA [o]	x	As clinically indicated	C1, D15 and every 4 cycles thereafter	x [o]
Atezolizumab administration [p]		x		
Trastuzumab emtansine administration [q]		x		
Response Assessments [r, s]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [t]		Submit within 21 days of C1, D1		

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Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 to −1 [A]	(±3)	(±3)	≤ 28 days *after* last study dose
Whole blood samples [u]	x		see footnote u	
Adverse events [v]	x	Collected on an ongoing basis		*x* [v]
Concomitant Medications [w]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; PET=positron emission tomography; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC, chemistry panel, and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-trastuzumab emtansine discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive ERBB2 gene mutation or amplification plus TMB-H/MSI-H/dMMR status should occur prior to performing other trial-related eligibility assessments. TMB-H should be determined using a tissue-based NGS assay.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes INR and aPTT.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] LVEF assessments will occur during the screening period, and on Day 15 of Cycle 1, and every fourth cycle thereafter (e.g. C5D15, C9D15, etc.). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed >28 days before last study treatment administration and if no post-treatment evaluation was performed. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[p] Atezolizumab will be administered first by IV infusion at a dose of 1200 mg on Cycle 1, and on Day 1 of each 21-day cycle thereafter. For the first infusion of atezolizumab, vital signs should be determined within 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes

after the infusion, if clinically indicated. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.

[q] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Day 1 of Cycle 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[r] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[s] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors)(or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[t] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[u] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of trastuzumab emtansine or 90 days after the final dose of atezolizumab, whichever is longer. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-trastuzumab emtansine discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study treatment.

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Appendix 20
Arm K: Ipatasertib plus Atezolizumab in Patients with PI3K (PIK3CA) Activating Mutation-Positive Tumors

21. ARM K: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PI3K (PIK3CA) ACTIVATING MUTATION-POSITIVE TUMORS

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K.4 MATERIALS AND METHODS

K.4.1 Patients

To be enrolled in Arm K: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

K.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm K: ipatasertib plus atezolizumab treatment:

- PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  - H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V
  - Other activating mutations with Medical Monitor approval
- No available acceptable treatment for malignancy that is expected to provide clinical benefit
- ANC $\geq$ 1000/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least

28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period. See detailed contraception requirements in Appendix 2.

- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

K.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm K: ipatasertib plus atezolizumab treatment:

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

  Use of an indwelling catheter (e.g., PleurX®) is allowed.

- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 enrollment.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
  - 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.

- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor
  - Up to approximately 12 such patients may be enrolled
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose

corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Prior treatment with ipatasertib or other Akt inhibitors
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$2 weeks prior to initiation of study treatment are eligible for enrollment.

  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.
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Appendix 7)

K.4.2 Study Treatment

Study treatment in this arm will consist of ipatasertib in combination with atezolizumab.

K.4.2.1 Formulation and Packaging

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets.

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

Atezolizumab 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.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access.

K.4.2.2 Dosage, Administration, and Compliance for Ipatasertib

Study treatment will be administered in 21 day cycles.

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression or intolerable toxicity (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

The tablets will be swallowed whole (not chewed) with 3 ounces (90 mL) of fluid. *Ipatasertib is recommended to be taken at least 2 hours after the last meal of the day, and patients should refrain from eating overnight*. Patients are required to receive prophylaxis with loperamide throughout the first cycle (2 mg oral twice a day, or per local institutional guidelines) and at subsequent cycles as clinically indicated (see Table 3).

For ipatasertib doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 8 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for ipatasertib dosage modification and treatment interruption or discontinuation are provided in Section K.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

K.4.2.3 Dosage, Administration, and Compliance for Atezolizumab

Study treatment will be administered in 21 day cycles.

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion, except as outlined in Section K.4.2.3. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a] • 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. [a] • 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 measured within 60 minutes prior to the infusion. [a] • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

No dose modification for atezolizumab is allowed. Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section E.5.2.2.7 for atezolizumab.

Owing to the risk of rash in Cycle 1, patients should receive the following prophylaxis during the first cycle when study treatments will be given (see Table 3 for AE management of dermatological toxicities, including rash):

- Unless contraindicated, daily PO antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine).
- On day when patients will receive atezolizumab, patients should receive at least 10 mg/day of prednisone (or equivalent dosing of other steroids e.g., methylprednisolone, prednisolone) as premedication prior to atezolizumab, followed by a fixed dose of 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated.

K.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

K.4.3.1 Permitted Therapy

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

- Oral contraceptives, as allowed per local guidelines
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy. Treatment with ipatasertib should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For a single fraction of radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Prophylaxis use of loperamide is mandated in the first cycle and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Table 3; please refer to that table for additional details. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.
- Prophylaxis use of antihistamines and prednisone (or equivalent dosing of other steroids) is mandated in the first cycle due to the risk of rash and is described in Section K.4.2.3.
- Granulocyte colony-stimulating factor treatment is permitted. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011)
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) is allowed. Both types of agents have potential immunomodulatory properties, but may be used as clinically indicated.

- Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section K.4.3.3)
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Stable dose of calcium-channel blockers are permitted.
- Stable dose of β-blockers, if an alternative treatment cannot be used, are permitted with caution.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per institutional practice. For example, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; seeAppendix 6).

K.4.3.2 Cautionary Therapy

K.4.3.2.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids 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 or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section K.5.2.2.3 [combination therapy] or Section E.5.2.2 [single agent]for guidelines for managing specific adverse events).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events associated with ipatasertib (refer to Section K.5.2.2.3 [combination therapy] or Section D.5.2.2.6, Section D.5.2.2.7 [single agent] for guidelines for managing specific adverse events). If daily systemic corticosteroids are initiated for treatment of any toxicity or other condition, they must be tapered to ≤10 mg/day of oral prednisone or equivalent before ipatasertib or atezolizumab can be resumed. Steroids used as prophylaxis (i.e., as premedication prior to scans, or as protocol-directed rash prophylaxis) do not require holding of ipatasertib or atezolizumab. Steroids used on a single day to manage infusion-related reactions (IRRs) or allergic reactions similarly do not require holding of ipatasertib.

K.4.3.2.2 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 all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

K.4.3.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug−drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

K.4.3.2.4 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 DDI study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state ipatasertib dosed at 600 mg QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug−drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from a clinical study showed that ipatasertib exposures were reduced by ~50% when co-administered with enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures significantly.

Therefore, strong CYP3A4/5 inhibitors or inducers or CYP3A4/5 substrates with a narrow therapeutic index should be avoided or used with caution (see Appendix 7). Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment

(i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

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

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

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

K.4.3.3 Prohibited Therapy

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 K.4.3.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in Section K.4.3.2.4)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment,
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited

during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients who require short-term use of moderate CYP3A4 inhibitors may continue study treatment 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 [FDA]): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

K.4.3.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit, potent CYP3A4 enzyme inhibitors, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

K.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the Arm K: ipatasertib plus atezolizumab treatment. Refer to the schedule of activities (see Section K.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation panel: INR and aPTT
- HbA1c, blood glucose (fasting)
- Amylase, lipase (fasting)
- Lipid panel (fasting): total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
- 12-lead electrocardiogram

K.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm K: ipatasertib plus atezolizumab treatment.

K.5.1 Risks Associated with Ipatsertib and Atezolizumab

K.5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity. Refer to the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

K.5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *peridardial 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 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

K.5.1.3 Risks Associated with Combination Use of Ipatasertib and Atezolizumab

On the basis of the frequency of adverse events associated with either ipatasertib or atezolizumab, the following adverse events are potential overlapping toxicities associated with combination use of ipatasertib and atezolizumab: diarrhea, colitis, hepatotoxicity, rash, pneumonitis, and hyperglycemia.

K.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

K.5.2.1 Dose Modifications and Interruptions

K.5.2.1.1 Dose Modifications and Interruptions for Ipatasertib

If the patient does not tolerate the QD dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient (i.e., doses below 200 mg/day of ipatasertib) will be allowed (see Table 2). Dose re-escalation is not permitted for ipatasertib.

If needed, dose reductions may occur in decrements of 100 mg and no more than two dose reductions will be allowed. Accordingly, the possible daily doses of ipatasertib are shown in Table 2. If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

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

Table 2 Ipatasertib Dose Reductions

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

Note: After dose reduction, the dose of ipatasertib may not be re-escalated.

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor consultation. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days, study drug may be restarted. 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.

If either ipatasertib or atezolizumab is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit. *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.

K.5.2.1.2 Dose Modifications and Interruptions for Atezolizumab

No dose reductions for atezolizumab are allowed. Interruptions to atezolizumab treatment are described in Section E.5.2.1.1.

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

K.5.2.2 Guidelines for Management of Specific Adverse Events

K.5.2.2.1 Guidelines for Management of Specific Adverse Events Associated with Ipatasertib

Guidelines for management of specific adverse events for ipatasertib given as a single agent are provided in Section D.5.2.2.

K.5.2.2.2 Guidelines for Management of Specific Adverse Events Associated with Atezolizumab

Guidelines for management of specific adverse events for atezolizumab given as a single agent are provided in Section E.5.2.2.

K.5.2.2.3 Guidelines for Management of Specific Adverse Events Associated with Ipatasertib plus Atezolizumab

Guidelines for the management of patients who experience adverse events are provided in Section E.5.2.2, and Table 3, as outlined below:

- Section E.5.2.2 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, ocular, pancreatic, neurologic disorders *(including facial paresis),* myocarditis, *myelitis, pericardial disorders,* meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Section E.5.2.2 and that ipatasertib be withheld or discontinued per the guidelines in Table 3.
- Table 3 provides guidelines for the management of patients who experience the following potential overlapping toxicities: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table 3. For these potential overlapping toxicities guidelines in Table 3, should be followed instead of guidelines in Section E.5.2.2.

- Table 3 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 3.

For cases in which management guidelines are not covered in Table 3 or Section E.5.2.2, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Ipatasertib plus Atezolizumab

Event	Management
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in Section E.5.2.2 • Withhold ipatasertib. • For anaphylaxis precautions, see Appendix 6. • For severe hypersensitivity reactions, permanently discontinue ipatasertib and atezolizumab.
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	• Follow guidelines for atezolizumab in Section E.5.2.2. • Withhold ipatasertib and contact *the* Medical Monitor for guidance.
Gastrointestinal toxicity	
General guidance	• 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Management
Gastrointestinal toxicity (cont.)	
General guidance	• 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 (taken 2 mg twice a day or per local institutional standard), 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. – 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 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).

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or Grade 2	• Continue ipatasertib and atezolizumab – Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate. • *For Grade 2 events, withhold atezolizumab and consider empiric steroids in case of strong suspicion for immune-mediated colitis while waiting for definitive diagnosis. Interrupt ipatasertib until diarrhea improves to Grade ≤ 1. Ipatasertib can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to Grade ≤ 1.*
Diarrhea, Grade 2 (persisting ≥ 5 days) or 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 strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • If event resolves to Grade 1 or better within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor. [a, b, c] • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level or discontinue ipatasertib permanently per *the* Medical Monitor.
Diarrhea, Grade 4	• Permanently discontinue ipatasertib and atezolizumab 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 *a confirmatory* biopsy if appropriate.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Management
Gastrointestinal toxicity (cont.)	
Colitis, Grade 1	• Continue ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • *For Grade 2 events, withhold atezolizumab and consider empiric steroids in case of strong suspicion for immune-mediated colitis while waiting for definitive diagnosis.* • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for >5 days.
Colitis, Grade 2	• Withhold ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. *If 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 ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab 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 4	• Permanently discontinue ipatasertib and atezolizumab 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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Management
Endocrine disorders	
Grade 1 hypothyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Grade 2 hypothyroidism	• *Follow guidelines provided in Section E.5.2.2.* • *Continue ipatasertib.*
Grade 3 and 4 hypothyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib. **TSH <0.1 mU/L:** • Follow guidelines for *Grade 3-4 hyperthroidism*.
Grade 2 hyperthyroidism	• *Follow guidelines provided in Section E.5.2.2.* • *Continue ipatasertib.*
Grade 3 and 4 hyperthyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib. • For life-threatening immune-related hyperthyroidism, withhold ipatasertib. If event becomes clinically manageable within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Hypophysitis (pan-hypopituitarism), Grade 4	• Follow guidelines provided in Section E.5.2.2. • Withhold ipatasertib until Grade ≤2.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Endocrine disorders (cont.)	
Hyperglycemia, any grade	• All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects. • 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-GADD45 antibody. • Hyperglycemia should be treated per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia, Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue ipatasertib and atezolizumab. • 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, Fasting glucose value > ULN to 250 mg/dL (> 8.9–13.9 mmol/L)	• Continue atezolizumab, consider interruption of ipatasertib. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 ful 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 t investigator. The Medical Monitor is available to advise as needed.

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Event	Management
Endocrine disorders (cont.)	
Hyperglycemia, Glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Withhold ipatasertib and atezolizumab dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • If the fasting hyperglycemia resolves to ≤ 160 mg/dL within 3 days, ipatasertib may be resumed at the previous dose level. • If the fasting hyperglycemia does not resolve to ≤ 160 mg/dL within 3 days or if fasting hyperglycemia ≥ 250 mg/dL recurs within 14 days, the dose of ipatasertib should be reduced by one dose level (Table 2) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperglycemia, Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Withhold ipatasertib and atezolizumab dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤ 160 mg/dL, ipatasertib should be reduced by one dose level (Table 2) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If hyperglycemia > 500 mg/dL recurs, permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Management
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	• Continue ipatasertib and atezolizumab. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Withhold ipatasertib and atezolizumab. • 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 ipatasertib and atezolizumab 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 at current dose. [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 ipatasertib and atezolizumab and contact *the* Medical Monitor. [c] • *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 IV methylprednisolone • 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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

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Event	Management
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue ipatasertib and atezolizumab.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue ipatasertib and atezolizumab. • 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. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor. [a, b, c]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue ipatasertib and atezolizumab. • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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Event	Management
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold ipatasertib and atezolizumab. • 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 ipatasertib and atezolizumab for life-threatening hepatic events and contact the Medical Monitor.
AST/ALT > 10 × ULN	• Permanently discontinue ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Arm K: Ipatasertib plus Atezolizumab in Patients with PI3K (PIK3CA) Activating Mutation-Positive Tumors

Event	Management
Dermatologic toxicity	
General guidance	• Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Unless contraindicated, a daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (e.g. loratadine, cetirizine, fexofenadine) and longer-acting formulated be used. • For the first 28-day cycle of ipatasertib plus atezolizumab: On days when patients will receive atezolizumab ($Day\ 1$), patients should received at least 10 mg prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2-4 consecutive days thereafter, unless contraindicated. • Ipatasertib should be permanently discontinued for rash-associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasetib are shown below. • Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab and atezolizumab should be permanently discontinued for confirmed cases.
Dermatologic event, Grade 1	• Consider referring patient to a dermatologist. • Continue ipatasertib and atezolizumab. • 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 higher steroid dose may be necessary as clinically indicated. • Ipatasertib: interrupt ipatasertib treatment until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. If steroid dose is ≤ 10 mg/day, ipatasertib may be resumed if clinically appropriate. • Atezolizumab: If steroid dose is ≤ 10 mg/day, atezolizumab should be continued.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on $the\ investigator's$ 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. The Medical Monitor is available to advise as needed.

Arm K: Ipatasertib plus Atezolizumab in Patients with PI3K (PIK3CA) Activating Mutation-Positive Tumors

Event	Management
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 3	• Withhold ipatasertib and atezolizumab. • Refer patient to dermatologist. Perform a biopsy if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent. • If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1–2 mg/kg/day. • Atezolizumab: if event resolves to Grade ≤ 1 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact *the* Medical Monitor. Only restart atezolizumab if steroid dose is ≤ 10 mg/day. [a, b, c] • Ipatasertib: if event resolves to Grade ≤ 1 or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level after discussion with *the* Medical Monitor. Only restart ipatasertib if steroid dose is ≤ 10 mg/day. If not, permanently discontinue ipatasertib.
Dermatologic event, Grade 4	• Permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor. [c]
Ipatasertib–related toxicities not described above	
Grade 3	• Withhold ipatasertib. Continue atezolizumab. • If event resolves to Grade 1 or baseline within 28 days and *the* Medical Monitor agrees that ipatasertib should be continued, resume ipatasertib. If not, permanently discontinue ipatasertib.
Grade 4	• Withhold ipatasertib and atezolizumab. • If event resolves to Grade 1 or baseline within 28 days and *the* Medical Monitor agrees that ipatasertib should be continued, resume ipatasertib. If not, permanently discontinue ipatasertib. • If event improves and *the* Medical Monitor agrees that atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

K.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients taking ipatasertib plus atezolizumab arm:

Ipatasertib

- Grade ≥3 fasting hyperglycemia
- Grade ≥3 hepatotoxicity
- Grade ≥3 ALT/AST elevations
- Grade ≥2 colitis/enterocolitis
- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis

Atezolizumab

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

K.5.4 Selected Adverse Events

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

- Diarrhea
- Asthenia (fatigue)
- Nausea

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

K.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 to −1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive PIK3CA activating mutation status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
Coagulation panel [l]	x			x
Fasting lipid panel, amylase, lipase [m]	x	x		x
Fasting HbA_{1C} [m]	x	x		x
Fasting blood glucose [n]	x	x	Weekly during C1	x
TSH, free T3 (or total T3), free T4 [o]	x	C1, D1 and every 3 cycles thereafter		
ECG [p]	x	As clinically indicated		x
ECHO or MUGA [q]	x	As clinically indicated		
Atezolizumab administration [r, s]		x		
Ipatasertib dispensing		x		
Ipatasertib compliance assessment [t]		x		x
Prophylaxis anti-diarrheal [u]		Every day of C1 and as clinically indicated		

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Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Prophylaxis with 10 mg of prednisone (or equivalent) [v]		D1 and 2-4 consecutive days after for C1only		
Daily antihistamine prophylaxis [v]		Every day of C1		
Response assessments [w, x]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [y]		Submit within 21 days of C1, D1		
Whole blood samples [z]	x		See footnote z	
Adverse events [aa]	x	Collected on an ongoing basis		*x* [aa]
Concomitant Medications [bb]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC, chemistry panel, and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1, with the exception of glucose, which should be drawn within 3 days prior. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post ipatasertib discontinuation or 90 days post-atezolizumab discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

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[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive PIK3CA activating mutation status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1 with the exception of glucose, which should be drawn within 3 days prior. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] Fasting lipid panel (cholesterol, triglyceride, HDL, and LDL), amylase, lipase, and HbA1c will be assessed after ≥8 hours of fasting. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[n] Samples should be assessed weekly during the first Cycle and D1 at every other cycle. Mid-cycle fasting glucose levels may be obtained by glucometer (fingerstick). If measurements are done at home, phone visits with site staff should be conducted to review results and assess any potential signs or symptoms of hyperglycemia.

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

[p] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[q] LVEF assessment by ECHO or MUGA to be performed at screening and as clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[r] The initial infusion 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.Refer to Section K.4.2.3 for details on atezolizumab infusions (including measurement of vital signs).

[s] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

[t] Ipatasertib is administered 400 mg PO QD. On Day 1 of each cycle, review compliance from previous cycle and dispense ipatasertib for next cycle.

[u] Loperamide 2 mg BID or equivalent or per local institutional guideline 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.

[v] For the first cycle only: On day when patients will receive atezolizumab, patients should receive at least 10 mg/day prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and a longer-acting formulation be used.

[w] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[x] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[y] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[z] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[aa] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[bb] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

K.7 REFERENCES

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Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Appendix 21
Arm L: Ipatasertib plus Atezolizumab in Patients with PTEN Loss/ Loss-of-Function or AKT Mutation-Positive Tumors

22. ARM L: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PTEN LOSS/ LOSS-OF-FUNCTION OR AKT ACTIVATING MUTATION-POSITIVE TUMORS

TABLE OF CONTENTS

L.4 MATERIALS AND METHODS

L.4.1 Patients

To be enrolled in Arm L: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

L.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm L: ipatasertib plus atezolizumab treatment:

- AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  - AKT1: E17K; L52R; Q79K
  - AKT2: E17K
  - AKT3: E17K; L51R; Q78K

  or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay (See Appendix 1 for details)
- No available acceptable treatment for malignancy that is expected to provide clinical benefit
- ANC $\geq$ 1000/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period. See detailed contraception requirements in Appendix 2.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a

failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

L.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm L: ipatasertib plus atezolizumab treatment:

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

  Use of an indwelling catheter (e.g., PleurX®) is allowed.

- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 enrollment.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
    - 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.

- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor
  - Up to approximately 12 such patients may be enrolled
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins

- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Prior treatment with ipatasertib or other Akt inhibitors
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$2 weeks prior to initiation of study treatment are eligible for enrollment.

  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.
- Grade $\geq$2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Appendix 7)

L.4.2 Study Treatment

Study treatment in this arm will consist of ipatasertib in combination with atezolizumab.

L.4.2.1 Formulation and Packaging

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets.

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

Atezolizumab 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.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access.

L.4.2.2 Dosage, Administration, and Compliance for Ipatasertib

Study treatment will be administered in 21-day cycles.

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression or intolerable toxicity (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

The tablets will be swallowed whole (not chewed) with 3 ounces (90 mL) of fluid. *Ipatasertib is recommended to be taken at least 2 hours after the last meal of the day, and patients should refrain from eating overnight*. Patients are required to receive prophylaxis with loperamide throughout the first cycle (2 mg oral twice a day, or per local institutional guidelines) and at subsequent cycles as clinically indicated (see Table 3).

For ipatasertib doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 8 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for ipatasertib dosage modification and treatment interruption or discontinuation are provided in Section L.5.2.1.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

L.4.2.3 Dosage, Administration, and Compliance for Atezolizumab

Study treatment will be administered in 21-day cycles.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizuamb infusion except as outlined in Section L.4.2.3 for the purpose of preventing rash. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a] • 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. [a] • 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 measured within 60 minutes prior to the infusion. [a] • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

No dose modification for atezolizumab is allowed. Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section E.5.2.2.7 for atezolizumab.

Owing to the risk of rash in Cycle 1, patients should receive the following prophylaxis during the first cycle when study treatments will be given (see Table 3 for AE management of dermatological toxicities, including rash):

- Unless contraindicated, daily PO antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine).
- On day when patients will receive atezolizumab, patients should receive at least 10 mg/day of prednisone (or equivalent dosing of other steroids e.g., methylprednisolone, prednisolone) as premedication prior to atezolizumab, followed by a fixed dose of 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated.

L.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

L.4.3.1 Permitted Therapy

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

- Oral contraceptives, as allowed per local guidelines
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy. Treatment with ipatasertib should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For a single fraction of radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Prophylaxis use of loperamide is mandated in the first cycle and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Table 3; please refer to that section for additional details. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.
- Prophylaxis use of antihistamines and prednisone (or equivalent dosing of other steroids) is mandated in the first cycle due to the risk of rash and is described in Section L.4.2.3.
- Granulocyte colony-stimulating factor treatment is permitted. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011)
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis,

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

- Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section L.4.3.3)
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Stable dose of calcium-channel blockers are permitted.
- Stable dose of β-blockers, if an alternative treatment cannot be used, are permitted with caution.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per institutional practice. For example, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6).

L.4.3.2 Cautionary Therapy

L.4.3.2.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids 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 or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section L.5.2.2.3

[combination therapy] and Section E.5.2.2 [single agent]for guidelines for managing specific adverse events).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events associated with ipatasertib (refer to Section L.5.2.2.3 [combination therapy] or Section D.5.2.2.6, Section D.5.2.2.7 [single agent] for guidelines for managing specific adverse events). If daily systemic corticosteroids are initiated for treatment of any toxicity or other condition, they must be tapered to ≤10 mg/day of oral prednisone or equivalent before ipatasertib or atezolizumab can be resumed. Steroids used as prophylaxis (i.e., as premedication prior to scans, or as protocol-directed rash prophylaxis) do not require holding of ipatasertib or atezolizumab. Steroids used on a single day to manage infusion-related reactions (IRRs) or allergic reactions similarly do not require holding of ipatasertib.

L.4.3.2.2 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 all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

L.4.3.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug−drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

L.4.3.2.4 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 (DDI) study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state ipatasertib dosed at 600 mg QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug−drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from a clinical study showed that ipatasertib exposures were reduced by ~50% when co-administered with enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures significantly.

Therefore, strong CYP3A4/5 inhibitors or inducers or CYP3A4/5 substrates with a narrow therapeutic index should be avoided or used with caution (see Appendix 7). Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment

(i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

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

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

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

L.4.3.3 Prohibited Therapy

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 L.4.3.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in Section L.4.3.2.4)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment,
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because

these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients who require short-term use of moderate CYP3A4 inhibitors may continue study treatment 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 [FDA]):
> http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

L.4.3.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit, potent CYP3A4 enzyme inhibitors, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

L.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the Arm L: ipatsertib plus atezolizumab treatment. Refer to the schedule of activities (Section L.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation panel: INR and aPTT
- HbA1c, blood glucose (fasting)
- Amylase, lipase (fasting)

- Lipid panel (fasting): total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
- 12-lead electrocardiogram

L.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm L: ipatatsertib plus atezolizumab treatment

L.5.1 Risks Associated with Ipatasertib and Atezolizumab

L.5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity. Refer to the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

L.5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *peridardial 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 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

L.5.1.3 Risks Associated with Combination Use of Ipatasertib and Atezolizumab

On the basis of the frequency of adverse events associated with either ipatasertib or atezolizumab, the following adverse events are potential overlapping toxicities associated with combination use of ipatasertib and atezolizumab: diarrhea, colitis, hepatotoxicity, rash, pneumonitis, and hyperglycemia.

L.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

L.5.2.1 Dose Modifications and Interruptions

L.5.2.1.1 Dose Modifications and Interruptions for Ipatasertib

If the patient does not tolerate the QD dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient (i.e., doses below 200 mg/day of ipatasertib) will be allowed (see Table 2). Dose re-escalation is not permitted for ipatasertib.

If needed, dose reductions may occur in decrements of 100 mg and no more than two dose reductions will be allowed. Accordingly, the possible daily doses of ipatasertib are shown in Table 2. If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

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

Table 2 Ipatasertib Dose Reductions

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

Note: After dose reduction, the dose of ipatasertib may not be re-escalated.

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor consultation. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days, study drug may be restarted. 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.

If either ipatasertib or atezolizumab is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit. *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.*

L.5.2.1.2 Dose Modifications and Interruptions for Atezolizumab

No dose reductions for atezolizumab are allowed. No dose reductions for atezolizumab are allowed. Interruptions to atezolizumab treatment are described in Section E.5.2.1.1.

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

L.5.2.2 Guidelines for Management of Specific Adverse Events

L.5.2.2.1 Guidelines for Management of Specific Adverse Events Associated with Ipatasertib

Guidelines for management of specific adverse events for ipatasertib given as a single agent are provided in Section D.5.2.2.

L.5.2.2.2 Guidelines for Management of Specific Adverse Events Associated with Atezolizumab

Guidelines for management of specific adverse events for atezolizumab given as a single agent are provided in Section E.5.2.2.

L.5.2.2.3 Guidelines for Management of Specific Adverse Events Associated with Ipatasertib plus Atezolizumab

Guidelines for the management of patients who experience adverse events are provided in Section E.5.2.2 and Table 3, as outlined below:

- Section E.5.2.2 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, ocular, pancreatic, neurologic disorders *(including facial paresis),* myocarditis, *myelitis, pericardial disorders,* meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Section E.5.2.2 and that ipatasertib be withheld or discontinued per the guidelines in Table 3.
- Table 3 provides guidelines for the management of patients who experience the following potential overlapping toxicities: gastrointestinal, dermatologic, hepatic,

pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table 3. For these potential overlapping toxicities, guidelines in Table 3 should be followed instead of guidelines in Section E.5.2.2.

- Table 3 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 3.

For cases in which management guidelines are not covered in Table 3 or Section E.5.2.2, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Ipatasertib plus Atezolizumab

Event	Management
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in Section E.5.2.2 • Withhold ipatasertib. • For anaphylaxis precautions, see Appendix 6. • For severe hypersensitivity reactions, permanently discontinue ipatasertib and atezolizumab.
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	• Follow guidelines for atezolizumab in Section E.5.2.2. • Withhold ipatasertib and contact *the* Medical Monitor for guidance.
Gastrointestinal toxicity	
General guidance	• 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Gastrointestinal toxicity (cont.)	
General guidance	• 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 (taken 2 mg twice a day or per local institutional standard), 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. – 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 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).

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or Grade 2	• Continue ipatasertib and atezolizumab – Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate. • *For Grade 2 events, withhold atezolizumab and consider empiric steroids in case of strong suspicion for immune-mediated colitis while waiting for definitive diagnosis. Interrupt ipatasertib until diarrhea improves to Grade ≤1. Ipatasertib can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to Grade ≤1.*
Diarrhea, Grade 2 (persisting ≥5 days) or 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 strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • If event resolves to Grade 1 or better within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab and contact Medical Monitor. [a, b, c] • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level or discontinue ipatasertib permanently per *the* Medical Monitor.
Diarrhea, Grade 4	• Permanently discontinue ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Gastrointestinal toxicity (cont.)	
Colitis, Grade 1	• Continue ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • *For Grade 2 events, withhold atezolizumab and consider empiric steroids in case of strong suspicion for immune-mediated colitis while waiting for definitive diagnosis.* • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for >5 days.
Colitis, Grade 2	• Withhold ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. *If 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 ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab 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 4	• Permanently discontinue ipatasertib and atezolizumab 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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Endocrine disorders	
Grade 1 hypothyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Grade 2 hypothyroidism	• *Follow guidelines provided in Section E.5.2.2.* • *Continue ipatasertib.*
Grade 3 and 4 hypothyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib. **TSH <0.1 mU/L:** • Follow guidelines for *Grade 3–4 hyperthroidism*.
Grade 2 hyperthyroidism	• *Follow guidelines provided in Section E.5.2.2.* • *Continue ipatasertib.*
Grade 3 and 4 hyperthyroidism	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib. • For life-threatening immune-related hyperthyroidism, withhold ipatasertib. If event becomes clinically manageable within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Follow guidelines provided in Section E.5.2.2. • Continue ipatasertib.
Hypophysitis (pan-hypopituitarism), Grade 4	• Follow guidelines provided in Section E.5.2.2. • Withhold ipatasertib until Grade ≤2.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Endocrine disorders (cont.)	
Hyperglycemia, any grade	• All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects. • 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-GADD45 antibody. • Hyperglycemia should be treated per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia, Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue ipatasertib and atezolizumab. • 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, Fasting glucose value > ULN to 250 mg/dL (> 8.9–13.9 mmol/L)	• Continue atezolizumab, consider interruption of ipatasertib. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 b the investigator. The Medical Monitor is available to advise as needed.

Event	Management
Endocrine disorders (cont.)	
Hyperglycemia, Glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Withhold ipatasertib and atezolizumab dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • If the fasting hyperglycemia resolves to ≤ 160 mg/dL within 3 days, ipatasertib may be resumed at the previous dose level. • If the fasting hyperglycemia does not resolve to ≤ 160 mg/dL within 3 days or if fasting hyperglycemia ≥ 250 mg/dL recurs within 14 days, the dose of ipatasertib should be reduced by one dose level (Table 2) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperglycemia, Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Withhold ipatasertib and atezolizumab dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • The patient should adopt a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤ 160 mg/dL, ipatasertib should be reduced by one dose level (Table 2) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If hyperglycemia > 500 mg/dL recurs, permanently discontinue ipatasertib and atezolizumab and contact the Medical Monitor.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on 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. The Medical Monitor is available to advise as needed.

Arm L: Ipatasertib plus Atezolizumab in Patients with PTEN Loss/Loss-of-Function or AKT Mutation–Positive Tumors

Event	Management
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	• Continue ipatasertib and atezolizumab. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Withhold ipatasertib and atezolizumab. • 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 ipatasertib and atezolizumab 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 at current dose. [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 ipatasertib and atezolizumab and contact *the* Medical Monitor. [c] • *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 IV methylprednisolone • 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

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

Arm L: Ipatasertib plus Atezolizumab in Patients with PTEN Loss/Loss-of-Function or AKT Mutation–Positive Tumors

Event	Management
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue ipatasertib and atezolizumab.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue ipatasertib and atezolizumab. • 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. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor. [a, b, c]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue ipatasertib and atezolizumab. • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue ipatasertib and atezolizumab 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.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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. The Medical Monitor is available to advise as needed.

Event	Management
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT $>3\times$ ULN with total bilirubin $>2\times$ ULN	• Withhold ipatasertib and atezolizumab. • 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 $\leq 3\times$ ULN with total bilirubin $\leq 2\times$ ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact *the* Medical Monitor. [a, b, c] • If event resolves to AST/ALT $\leq 3\times$ ULN with total bilirubin $\leq 2\times$ ULN within 28 days and corticosteroid dose $\leq$ 10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib. • Permanently discontinue ipatasertib and atezolizumab for life-threatening hepatic events and contact the Medical Monitor.
AST/ALT $>10\times$ ULN	• Permanently discontinue ipatasertib and atezolizumab 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 $\leq 3\times$ ULN with total bilirubin $\leq 2\times$ ULN, taper corticosteroids over $\geq$ 1 month.

BAL = bronchoscopic alveolar lavage; 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 $\geq$ 1 month to $\leq$ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., $>$12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of $\leq$10 mg/day oral prednisone. 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. The Medical Monitor is available to advise as needed.

Arm L: Ipatasertib plus Atezolizumab in Patients with PTEN Loss/Loss-of-Function or AKT Mutation–Positive Tumors

Event	Management
Dermatologic toxicity	
General guidance	• Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Unless contraindicated, a daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (e.g. loratadine, cetirizine, fexofenadine) and longer-acting formulated be used. • For the first 28-day cycle of ipatasertib plus atezolizumab: On days when patients will receive atezolizumab ($Day\ 1$), patients should received at least 10 mg prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2-4 consecutive days thereafter, unless contraindicated. • Ipatasertib should be permanently discontinued for rash-associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasetib are shown below. • Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab and atezolizumab should be permanently discontinued for confirmed cases.
Dermatologic event, Grade 1	• Consider referring patient to a dermatologist. • Continue ipatasertib and atezolizumab. • 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 higher steroid dose may be necessary as clinically indicated. • Ipatasertib: interrupt ipatasertib treatment until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. If steroid dose is ≤ 10 mg/day, ipatasertib may be resumed if clinically appropriate. • Atezolizumab: If steroid dose is ≤ 10 mg/day, atezolizumab should be continued.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on $the\ investigator's$ 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. The Medical Monitor is available to advise as needed.

Event	Management
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 3	• Withhold ipatasertib and atezolizumab. • Refer patient to dermatologist. Perform a biopsy if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent. • If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1–2 mg/kg/day. • Atezolizumab: if event resolves to Grade ≤ 1 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact *the* Medical Monitor. Only restart atezolizumab if steroid dose is ≤ 10 mg/day. [a, b, c] • Ipatasertib: if event resolves to Grade ≤ 1 or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level after discussion with *the* Medical Monitor. Only restart ipatasertib if steroid dose is ≤ 10 mg/day. If not, permanently discontinue ipatasertib.
Dermatologic event, Grade 4	• Permanently discontinue ipatasertib and atezolizumab and contact *the* Medical Monitor. [c]
Ipatasertib–related toxicities not described above	
Grade 3	• Withhold ipatasertib. Continue atezolizumab. • If event resolves to Grade 1 or baseline within 28 days and *the* Medical Monitor agrees that ipatasertib should be continued, resume ipatasertib. If not, permanently discontinue ipatasertib.
Grade 4	• Withhold ipatasertib and atezolizumab. • If event resolves to Grade 1 or baseline within 28 days and *the* Medical Monitor agrees that ipatasertib should be continued, resume ipatasertib. If not, permanently discontinue ipatasertib. • If event improves and *the* Medical Monitor agrees that atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab.

BAL = bronchoscopic alveolar lavage; 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 longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based *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. The Medical Monitor is available to advise as needed.

L.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients taking ipatasertib plus atezolizumab arm:

Ipatasertib

- Grade ≥3 fasting hyperglycemia
- Grade ≥3 hepatotoxicity
- Grade ≥3 ALT/AST elevations
- Grade ≥2 colitis/enterocolitis
- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis

Atezolizumab

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

L.5.4 Selected Adverse Events

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

- Diarrhea
- Asthenia (fatigue)
- Nausea
- Neutropenia (neutrophil count decreased, febrile neutropenia)

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

L.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 Days *After* Last Study Dose
Informed consent [d]	x			
Documentation of positive AKT activating mutation or PTEN loss/loss of function status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
Coagulation panel [l]	x			x
Fasting lipid panel, amylase, lipase [m]	x	x		x
Fasting HbA_{1C} [n]	x	x		x
Fasting blood glucose [n]	x	x	Weekly during C1	x
TSH, free T3 (or total T3), free T4 [o]	x	C1, D1 and every 3 cycles thereafter		
ECG [p]	x	As clinically indicated		x
ECHO or MUGA [q]	x	As clinically indicated		
Atezolizumab administration [r, s]		x		
Ipatasertib dispensing		x		

Arm L: Ipatasertib plus Atezolizumab in Patients with PTEN Loss/ Loss of Function or AKT Mutation-Positive Tumors

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 Days *After* Last Study Dose
Ipatasertib compliance assessment [t]		x		x
Prophylaxis anti-diarrheal [u]		Every day of C1 and as clinically indicated		
Prophylaxis with 10 mg of prednisone (or equivalent) [v]		D1 and 2-4 consecutive days after for C1 only		
Daily antihistamine prophylaxis [v]		Every day of C1		
Response assessments [w, x]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [y]		Submit within 21 days of C1, D1		
Whole blood samples [z]	x		See footnote z	
Adverse events [aa]	x	Collected on an ongoing basis		*x* [aa]
Concomitant Medications [bb]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC, chemistry panel, and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1, with the exception of glucose, which should be drawn within 3 days prior. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-

ipatasertib discontinuation or 90 days post-atezolizumab discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive AKT gene activating mutations or PTEN loss or loss of function status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1, with the exception of glucose, which should be drawn within 3 days prior. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] Fasting lipid panel (cholesterol, triglyceride, HDL, and LDL), amylase, lipase, and HbA1c will be assessed after $\geqslant$8 hours of fasting. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[n] Samples should be assessed weekly during the first Cycle and D1 at every other cycle. Mid-cycle fasting glucose levels may be obtained by glucometer (fingerstick). If measurements are done at home, phone visits with site staff should be conducted to review results and assess any potential signs or symptoms of hyperglycemia.

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

[p] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[q] LVEF assessment by ECHO or MUGA to be performed at screening and as clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[r] The initial infusion 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. Refer to Section L.4.2.3 for details on atezolizumab infusions (including measurement of vital signs).

[s] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

[t] Ipatasertib is administered 400 mg PO QD. On Day 1 of each cycle, review compliance from previous cycle and dispense ipatasertib for next cycle.

[u] Loperamide 2 mg BID or equivalent or per local institutional guideline 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.

[v] For the first cycle only: On day when patients will receive atezolizumab, patients should receive at least 10 mg/day prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and a longer-acting formulation be used.

[w] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[x] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[y] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[z] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[aa] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[bb] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

L.7 REFERENCES

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Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205

Appendix 22
Arm M: Ipatasertib plus Paclitaxel in Patients with Co-mutations in PI3K (PIK3CA) Activating Mutations and PTEN Loss/ Loss-of-Function or AKT Activating Mutation-Positive Tumors

23. ARM M: IPATASERTIB PLUS PACLITAXEL IN PATIENTS WITH CO-MUTATIONS IN PI3K (PIK3CA) ACTIVATING MUTATIONS AND PTEN LOSS/ LOSS-OF-FUNCTION OR AKT ACTIVATING MUTATION-POSITIVE TUMORS

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M.4 MATERIALS AND METHODS

M.4.1 Patients

To be enrolled in Arm M: ipatasertib in combination with paclitaxel treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

M.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm M: ipatasertib plus paclitaxel treatment:

- A co-mutation of either PI3K activating mutation and AKT activating mutation or a PI3K activating and PTEN loss or loss of function based on the following biomarkers:
  - PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

    PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

    - H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V
    - Other activating mutations with Medical Monitor approval

- AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  - AKT1: E17K; L52R; Q79K
  - AKT2: E17K
  - AKT3: E17K; L51R; Q78K

  or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay (See Appendix 1 for details)

- ANC $\geq$ 1500/μl within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 6 months after the last dose of paclitaxel, whichever occurs later, and agreement to refrain from donating eggs during this same period. See detailed contraception requirements in Appendix 2.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and 3 months after the last dose of paclitaxel, whichever occurs later and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

M.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm M: ipatasertib plus paclitaxel treatment:

- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of >10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Uncontrolled pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain
  - Patients requiring 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 $\geq$ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade $\leq$ 1) prior to study treatment initiation
  - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium, $>$ 12 mg/dL calcium, or corrected serum calcium $>$ ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade $\geq$2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Appendix 7)
- Prior treatment with an Akt inhibitor

Note that prior PI3K or mTOR inhibitors are allowed.

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

M.4.2 Study Treatment

Study treatment in this arm will consist of ipatasertib in combination with paclitaxel treatment.

M.4.2.1 Formulation and Packaging

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access.

For information on the packaging, handling and storage, see the Pharmacy Manual and Ipatasertib Investigator's Brochure.

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

M.4.2.2 Dosage, Administration, and Compliance for Ipatasertib

Study treatment will be administered on days 1 through 21 of 28-day cycles.

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) on days 1 through 21 of 28-day cycles until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The tablets will be swallowed whole (not chewed) with 3 ounces (90 mL) of fluid. *Ipatasertib is recommended to be taken at least 2 hours after the last meal of the day, and patients should refrain from eating overnight.* Patients are required to receive

prophylaxis (see Section M.5.2.4.1) with loperamide throughout the first cycle and at subsequent cycles as clinically indicated.

For ipatasertib doses to be administered at home, a sufficient number of tablets should be dispensed to the patient to last until the next visit, or at the investigator's discretion, through one cycle. Patients will be asked to record in a medication diary the time and date for each dose taken.

A missed dose can be taken within 8 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for ipatasertib dosage modification and treatment interruption or discontinuation are provided in Section M.5.2.1.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

M.4.2.3 Dosage, Administration, and Compliance for Paclitaxel

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. If the dose on Day 1, 8, or 15 is missed, it can be given on Day 22. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by $>$10% during the study, the body surface area and drug doses should be recalculated.

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

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine, and an H_2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, should be avoided.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

M.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

M.4.3.1 Permitted Therapy

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

- Oral contraceptives, as allowed per local guidelines
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy. Treatment with ipatasertib and paclitaxel should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For a single fraction of radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. The patient may continue ipatasertib plus paclitaxel treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Premedication with antihistamines, antipyretics, and/or analgesics for each paclitaxel administration as described in Section M.4.2.3
- Prophylaxis use of loperamide is mandated in the first cycle and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Section M.5.2.4.1; please refer to that section for additional details. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.
- Granulocyte colony-stimulating factor treatment is permitted. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011)
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis,

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

- Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per institutional practice. For example, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6).

M.4.3.2 Cautionary Therapy

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold may be shorter, if discussed by the investigator with the Medical Monitor. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events (refer to Section M.5.2.4.5 and Section M.5.2.4.6 for details). All study treatment should be temporarily held during systemic corticosteroids treatment (except when corticosteroids are given as pre-medication to paclitaxel).

M.4.3.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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

Therefore, strong CYP3A4/5 inhibitors or inducers or CYP3A4/5 substrates with a narrow therapeutic index should be avoided or used with caution (see Appendix 7). Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

- Paclitaxel exposures may be increased due to CYP2C8 inhibition; therefore, strong and moderate CYP2C8 inhibitors, such as gemfibrozil, teriflunomide, clopidogrel, and deferasirox should be used with caution during treatment with paclitaxel. Similarly, CYP2C8 inducers should be avoided or used with caution.

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

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

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

M.4.3.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug−drug interactions (DDIs) are

generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

M.4.3.3 Prohibited Therapy

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

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in Section M.4.3.2.1)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study 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 all study treatment should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients who require short-term use of moderate CYP3A4 inhibitors may continue study treatment 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 (FDA): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

M.4.3.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit, potent CYP3A4 enzyme inhibitors, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

M.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the Arm M: ipatasertib plus paclitaxel treatment. Refer to the schedule of activities (Section M.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Coagulation panel: INR and aPTT
- HbA1c, blood glucose (fasting)
- Amylase, lipase (fasting)
- Lipid panel (fasting): total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

Functional Assessments

- LVEF assessment: echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
- 12 lead electrocardiogram (ECG)

M.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm M: ipatasertib plus paclitaxel treatment.

M.5.1 Risks Associated with Ipatasertib and Paclitaxel

M.5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity. Refer to the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

M.5.1.2 Risks Associated with Paclitaxel

Paclitaxel has been associated with risks such as the following: Bone marrow suppression, neutropenia, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Additionally, reported adverse events which were less common are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test (LFT) elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other electrocardiogram (ECG) abnormalities, syncope, and venous thrombosis. For more details regarding the safety profile of paclitaxel, see the Paclitaxel Prescribing Information or Summary of Product Characteristics.

M.5.1.3 Risks Associated with Ipatasertib in Combination with Paclitaxel

Ipatasertib in combination with paclitaxel has been administered to 61 cancer patients in Study GO29227 (LOTUS). Adverse events related to ipatasertib/placebo whose incidences were higher by ≥10% in patients receiving ipatasertib+paclitaxel versus placebo+paclitaxel were diarrhea (93.4% vs. 21.0%) and nausea (52.5% vs. 33.9%). The most frequent Grade≥3 adverse events (reported in ≥5% of patients in either treatment arm) in patients in the ipatasertib+paclitaxel arm vs placebo + paclitaxel arm were diarrhea (14 patients [23.0%], all Grade 3, vs. 0 patients), neutropenia (6 patients [9.8%] vs. 1 patient [1.6%]), decreased neutrophil count (5 patients [8.2%] vs. 4 patients [6.5%]), and fatigue (2 patients [3.3 %] vs. 4 patients [6.5%]), respectively.

The incidence of overall neutropenia in the LOTUS Study was similar in both arms (34% in the ipatasertib+paclitaxel arm vs. 39% in the placebo+paclitaxel arm), but Grade ≥3 neutropenia, analyzed by grouped terms of similar medical concept, was higher in the ipatasertib+paclitaxel arm (18% vs. 8%). Thus, for recurrent Grade ≥ 3 neutropenia, ipatasertib should be reduced by one dose level when treatment is restarted (refer to the management guidelines in Section M.5.2.4).

Ipatasertib in combination with paclitaxel (N=146) and placebo with paclitaxel (N=76) were observed in cohort B of study CO40016. Adverse events related to ipatasertib/placebo whose incidences were higher by ≥10% in patients receiving ipatasertib+paclitaxel versus placebo+paclitaxel were diarrhea (84.8% vs 37.3%), nausea (41.4% vs 20.0%), peripheral neuropathy (31.7% vs 16.0%), vomiting (29.0% vs 6.7%) and rash (20.0% vs 12.0%). The most frequent Grade≥3 adverse events (reported in ≥5% of patients in either treatment arm) in patients in the ipatasertib+paclitaxel arm vs placebo + paclitaxel arm were diarrhea (11.7% vs 1.3%), decreased neutrophil count (9.0% vs 6.7%) neutropenia (8.3% vs 9.3), peripheral sensory neuropathy (2.8% vs 5.3%) and hypertension (1.4% vs 5.3%), respectively.

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

M.5.2 Guidelines for Management of Adverse Events

M.5.2.1 Dosage Modification and Interruptions

M.5.2.1.1 Dosage Modification and Interruptions for Ipatasertib

If the patient does not tolerate the QD dosing of the ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient (i.e., doses below 200 mg/day of ipatasertib) will be allowed (see Table 1). Dose re-escalation is not permitted for ipatasertib.

Table 1 Dose Reductions for Ipatasertib

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

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

Patients may hold the ipatasertib for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug. If the ipatasertib is discontinued at any time during the study, patients may have the option of continuing on study with paclitaxel alone.

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib and/or paclitaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor consultation. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days, study drug may be restarted after consultation with the Medical Monitor.

M.5.2.1.2 Dosage Modification and Interruptions for Paclitaxel

To manage paclitaxel-related toxicity, no more than one dose reduction for paclitaxel is allowed (Table 2). Paclitaxel doses other than specified in Table 2 will not be allowed.

Table 2 Dose Reductions for Paclitaxel

Dose Level [a]	Paclitaxel
Starting dose	80 mg/m^2
First dose reduction	65 mg/m^2
Second dose reduction	Not permitted
Third dose reduction	Not Applicable

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

If paclitaxel treatment is interrupted, consider delaying the ipatasertib and paclitaxel treatment concurrently for up to 7 days (i.e., shifting the 7 days-off week for ipatasertib so that 21 daily doses in every 28 days is maintained), at the discretion of the

investigator. The interrupted dose of paclitaxel may be administered later in the same cycle, ideally on Day 22, taking into consideration the paclitaxel dosing starting on Day 1 of the next cycle.

M.5.2.2 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib

Guidelines for management of specific adverse events for ipatasertib given as a single agent are provided in Section D.5.2.2**.**

M.5.2.3 Guidelines for Management of Patients Who Experience Specific Adverse Events with Paclitaxel

Toxicities associated or possibly associated with paclitaxel treatment should be managed according to standard medical practice and in accordance with the respective packaging insert.

M.5.2.4 Adverse Event Management Guidelines for Ipatasertib plus Paclitaxel

Guidelines for management of specific adverse events are provided in the subsections below.

M.5.2.4.1 Diarrhea Management Guidelines

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table 3. In this study, all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [Clostridium difficile, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of

diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines.

Dose intensity of paclitaxel should be maintained as tolerated. 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 Section M.5.2.1.1 and Table 1. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued. Paclitaxel dose reduction or discontinuation should be considered if diarrhea persists even after ipatasertib discontinuation.

Table 3 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients are mandated to receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance. If there are clinical concerns that preclude the use of loperamide prophylaxis in Cycle 1, discussion with the Medical Monitor is required. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.

Table 3 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib 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 o ne (or one additional) dose level (see Section M.5.2.1.1) for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 3 Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib and paclitaxel until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level (see Section M.5.2.1.1) when treatment is restarted. Consider resuming paclitaxel at the same dose. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level (see Section M.5.2.1.1). Consider reducing paclitaxel by one dose level when treatment is restarted (see Section M.5.2.1.2). • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Table 3 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib. • Interrupt paclitaxel until diarrhea improves to Grade 1 or better. Consider resuming paclitaxel by one dose level lower or discontinuing paclitaxel per investigator's discretion (see Section M.5.2.1.2).

ADL = activities of daily living; BID = twice a day; NCI CTCAE $v5$.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE $v5$.0, a disorder characterized by frequent and watery bowel movements.

M.5.2.4.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see Table 4) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Table 4 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) [a]	• Monitor fasting glucose per protocol • Consider initiating home glucose monitoring
Fasting glucose value > 160 to 250 mg/dL (> 8.9–13.9 mmol/L) [a]	• Interruption of ipatasertib until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Initiate home glucose monitoring • Start oral anti-diabetic medications (e.g., metformin). • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table 1). • 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.
Fasting glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) [a]	• Interrupt ipatasertib dosing until fasting hyperglycemia resolves to ≤ 160 mg/dL. • Initiate home glucose monitoring • Treat hyperglycemia as medically appropriate. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • If the patient is already on an oral anti-diabetic medication, ipatasertib 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 fasting hyperglycemia ≥ 250 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level when treatment is restarted.
Fasting glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences [a]	• Interrupt ipatasertib dosing until resolution to ≤ 160 mg/dL. • Treat hyperglycemia as medically appropriate. • Initiate home glucose monitoring • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduce ipatasertib by one dose level if and when treatment is restarted. • If hyperglycemia > 500 mg/dL recurs, permanently discontinue ipatasertib.

ULN=upper limit of normal.

[a] For all grades, the patient should receive education on a diabetic diet.

M.5.2.4.3 Neutropenia and/or Thrombocytopenia

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte

colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib and/or paclitaxel are outlined in Table 5.

Table 5 Neutropenia and Thrombocytopenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib may be continued at the original dose. Paclitaxel may be held and can then be administered at the previous dose, when ANC has recovered to ≥1500/μL and when the platelet count has recovered to ≥100,000/μL. If clinically appropriate based on the investigator's medical judgment, paclitaxel may be administered up to 14 days (2 doses), even with Grade 2 neutropenia, without a dose reduction, as long as G-CSF is used to manage the neutropenia. If the hematologic criteria do not recover to Grade 1 or better within the 14-day window of treating for ongoing Grade 2 neutropenia, the subsequent paclitaxel dose(s) must be held until recovery of hematological criteria to Grade 1 or better.
Grade 3	• Ipatasertib and paclitaxel should both be held until recovery to Grade 1 and if clinically appropriate based on the investigator's medical judgment to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: If recovery is to Grade 1, resume the original dose. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. If recovery is to Grade 2, follow the guidance above. – Recurrent episode: Ipatasertib and paclitaxel should be reduced by one dose level when treatment is restarted. If patient has had more than three Grade 3 neutropenia episodes on study, despite the above dose reduction to 65 mg/m^2, the paclitaxel dose should be permanently discontinued, but the patient may continue to receive ipatasertib following discussion with the Medical Monitor. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue paclitaxel but may continue ipatasertib following discussion with the Medical Monitor.

Table 5 Neutropenia and Thrombocytopenia Management Guidelines (Cont.)

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Febrile neutropenia and Grade 4 neutropenia	• Paclitaxel and ipatasertib should be held until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. First episode: Ipatasertib and paclitaxel should be reduced by one dose level when treatment is restarted. Recurrent episode: Ipatasertib and paclitaxel should be discontinued. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue paclitaxel and ipatasertib treatment.

ANC = absolute neutrophil count; G-CSF= Granulocyte-colony stimulating factor.

M.5.2.4.4 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see Table 6). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in Section M.5.2.1.1, Table 1, and Table 6).

Table 6 Nausea and Vomiting Management Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥ 3	• Interrupt ipatasertib and paclitaxel until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥ 3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level (see Section M.5.2.1.1) when treatment is restarted. Paclitaxel dose may be reduced by one level if recurrent Grade 3 nausea or vomiting occurs after dose reduction of ipatasertib has occurred (see Section M.5.2.1.2).

M.5.2.4.5 Rash

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in Table 7 (see Section M.5.2.1.1 and Table 1 for dose modifications).

Table 7 Rash Management Guidelines

Severity of Rash	Management Guideline
General guidance	• Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Unless contraindicated, a daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (e.g. loratadine, cetirizine, fexofenadine) and longer-acting formulated 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. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasetib are shown below.
Grade 1	• Consider referring patient to a dermatologist • Continue ipatasertib plus paclitaxel. • Initiate supportive care (e.g. topical corticosteroids and continue antihistamine administration) • Consider treatment with 10 mg/day oral prednisone or equivalent
Grade 2	• Consider referring patient to a dermatologist for evaluation and perform a biopsy, if appropriate • Continue topical corticosteroids and antihistamine administration. Consider treatment with 10 mg/day oral prednisone or equivalent; treatment with higher steroid dose may be necessary as clinically indicated • Ipatasertib: interrupt ipatasertib treatment until resolution to Grade ≤1 or the toxicity is no longer clinically significant. If steroid dose is ≤10 mg/day, ipatasertib may be resumed if clinically appropriate.
Grade 3	• Withhold ipatasertib and paclitaxel • Refer patient to dermatologist. Perform a biopsy if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent • If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1-2 mg/kg/day • Ipatasertib: if event resolves to Grade ≤1 or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level after discussion with Medical Monitor. Only restart ipatasertib if steroid dose is ≤10 mg/day. If not, permanently discontinue ipatasertib.
Grade 4	• Permanently discontinue ipatasertib and paclitaxel and contact Medical Monitor

M.5.2.4.6 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 8).

Table 8 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib and paclitaxel treatment until improvement to Grade 1 or better. Consider resuming ipatasertib and paclitaxel at same dose level or one dose level below (see Section M.5.2.1.1 and Section M.5.2.1.2) per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose (see Section M.5.2.1.1). Consider resuming paclitaxel at same dose or one dose below (see Section M.5.2.1.2) per investigator's assessment. • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days. Paclitaxel dose should be resumed at one dose level below previous dose (see Section M.5.2.1.2) or discontinued per investigator's assessment.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib and paclitaxel treatment until improvement to Grade 1 or better. Resume ipatasertib and paclitaxel at one dose level below previous dose (see Section M.5.2.1.1 and Section M.5.2.1.2) per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib and paclitaxel should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib and paclitaxel. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

M.5.2.4.7 Mucositis

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table 9.

Table 9 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level (see Section M.5.2.1.1). The dose of paclitaxel may be maintained or reduced by one level for subsequent cycles per investigator's discretion (see Section M.5.2.1.2).
Grade ≥ 3	• Hold ipatasertib and paclitaxel until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level (see Section M.5.2.1.1). The dose of paclitaxel may be maintained or reduced by one dose level for subsequent cycles per investigator's discretion (see Section M.5.2.1.2). • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel and ipatasertib.

M.5.2.4.8 Peripheral Neuropathy

If Grade ≥ 3 peripheral neuropathy attributable to paclitaxel develops in patients, paclitaxel should be held until the neuropathy recovers to Grade 2 or better, or resolution such that the peripheral neuropathy is no longer clinically significant. During this time, patients may continue ipatasertib at the discretion of the investigator. If the peripheral neuropathy recovers to Grade 2 or better within 4 weeks or resolution such that the peripheral neuropathy is no longer clinically significant, dosing of paclitaxel may resume reduced by one dose level (see Section M.5.2.1.2). If recovery of the peripheral neuropathy to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel but may continue the ipatasertib.

M.5.2.4.9 Hypersensitivity

If a hypersensitivity reaction due to infusion of paclitaxel develops in patients, treatment for the hypersensitivity reaction, including the possibility of rechallenging with the

attributable chemotherapy agent, in presence of premedication for paclitaxel should be administered as per institutional guidelines or at the discretion of the investigator. The patient may continue the other study treatment components not associated with the toxicity (i.e., ipatasertib).

M.5.2.4.10 Other Non-Hematologic Toxicities

If other Grade ≥3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib and/or paclitaxel may be held, depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either ipatasertib or paclitaxel). Grade ≥3 non-hematologic toxicity should be monitored at least weekly.

If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.

If the toxicity resolves to Grade 1 or better in 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines in Section M.5.2.1.

Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >4 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator and after discussion with the Medical Monitor.

For Grade ≥3 toxicities associated primarily with laboratory abnormalities only (e.g., elevation of ALT, AST, lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice.

M.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients taking ipatasertib plus paclitaxel:

- Grade ≥3 fasting hyperglycemia
- Grade ≥3 hepatotoxicity
- Grade ≥3 ALT/AST elevations
- Grade ≥2 colitis/enterocolitis

- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis

M.5.4 Selected Adverse Events

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

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

M.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	−28 to −1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of patients with co-mutations in PIK3CA activating mutations and PTEN loss/ loss-of-function or AKT activating mutation-positive tumors by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Weight [h]	x	x		
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x		x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation panel [m]	x			x
Fasting lipid panel, amylase, lipase [n]	x	x		x
Fasting HbA_{1C} [n]	x	x		x
Fasting blood glucose [o]	x	x	Weekly during C1	x
ECG [p]	x	As clinically indicated		x
ECHO or MUGA [q]	x	As clinically indicated		
Paclitaxel administration [r]		x	See footnote r	

Arm M: Ipatasertib plus Paclitaxel in Patients with Co-mutations in PI3K (PIK3CA) Activating Mutations and PTEN Loss/ Loss of Function or AKT Activating Mutation-Positive Tumors

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Ipatasertib dispensing		x		
Ipatasertib compliance assessment [s]		x		x
Prophylaxis anti-diarrheal [t]		Every day of Cycle 1 and as clinically indicated		
Response assessments [u, v]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [w]		Submit within 21 days of C1, D1		
Whole blood samples [x]	x		See footnote x	
Adverse events [y]	x	Collected on an ongoing basis		*x* [y]
Concomitant Medications [z]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the chemistry panel is obtained within 7 days of Cycle 1, Day 1 it does not have to be repeated on Day 1, with the exception of glucose, which should be drawn within 3 days prior. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard-of-care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive co-mutation in PI3K activating mutation AND AKT gene activating mutations or PTEN loss or loss of function status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1, with the exception of glucose, which should be drawn within 3 days prior. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 3 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes aPTT and INR.

[n] Fasting lipid panel (cholesterol, triglyceride, HDL, and LDL), amylase, lipase, and HbA1c will be assessed after ≥8 hours of fasting. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[o] Samples should be assessed weekly during the first Cycle and D1 at every other cycle. Mid-cycle fasting glucose levels may be obtained by glucometer (fingerstick). If measurements are done at home, phone visits with site staff should be conducted to review results and assess any potential signs or symptoms of hyperglycemia.

[p] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[q] LVEF assessment by ECHO or MUGA to be performed at screening and as clinically indicated. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform ECHO/MUGA scan for each individual patient.

[r] Paclitaxel is administered 80 mg/m^2 by IV infusion on days 1, 8, 15 of each 28-day cycle including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count. If the patient's weight changes by >10% from baseline during the study, the body surface area and drug doses of paclitaxel should be recalculated. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine and an H2-receptor blocker (i.e. ranitidine or famotidine) or per institutional practice. H2-receptor antagonist, such as cimetidine, which are known to inhibit cytochrome P450, should be avoided.

[s] Ipatasertib is administered 400 mg PO QD on Days 1-21 of each 28-day cycle. On Day 1 of each cycle, review compliance from previous cycle and dispense ipatasertib for next cycle.

[t] Loperamide 2 mg BID or equivalent or per local institutional guideline 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.

[u] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[v] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[w] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[x] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[y] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[z] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

M.7 REFERENCES

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Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205

Appendix 23
Arm N: Atezolizumab plus Tiragolumab in Patients with TMB-H/MSI-H/dMMR-Positive Tumors

24. ARM N: ATEZOLIZUMAB PLUS TIRAGOLUMAB IN PATIENTS WITH TMB-H/MSI-H/DMMR-POSITIVE TUMORS

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N.4 MATERIALS AND METHODS

N.4.1 Patients

To be enrolled in Arm N: atezolizumab plus tiragolumab treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

N.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm N: atezolizumab plus tiragolumab treatment:

- Documentation of one of the following biomarkers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified assay (tissue or blood):
  - Tumor mutational burden-high (TMB-H), defined as ≥ 10 mutations per megabase as determined by a tissue-based NGS assay
  - Microsatellite instability high (MSI-H)
  - Deficient mismatch repair (dMMR)
- ANC ≥ 1200/μL within 14 days prior to initiation of study treatment
- Lymphocyte count ≥ 500/μL
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2
- For patients not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the final dose of tiragolumab or 5 months after the last dose of atezolizumab, whichever is later; and agreement to refrain from donating eggs during this same period. Please see Appendix 2 for complete details on contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 90 days after the last dose of tiragolumab and agreement to refrain from donating sperm during this same period. See detailed contraception requirements in Appendix 2.

N.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm N: atezolizumab plus tiragolumab treatment:

- Primary CNS tumors with any of the following characteristics:
  - History of intracranial hemorrhage or spinal cord hemorrhage
  - Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1
- Metastases to the midbrain, pons, medulla, or spinal cord
- Uncontrolled tumor-related pain

  Patients requiring 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 enrollment. 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 currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ upper limit of normal [ULN])
- Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exception (note that this is more stringent than the core criteria outlined in Section 4.1.2):
  - Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- Positive epstein-barr virus (EBV) viral capsid antigen IgM test at screening

  An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid

antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of 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
    - 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.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (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
- Prior allogeneic stem cell or solid organ transplantation
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-TIGIT, anti-LAG3, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti-CTLA-4 treatment may be enrolled, provided the following requirements are met:
  - Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment
  - No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events [NCI CTCAE] Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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 (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- Any prior Grade $\geq$ 3 immune-mediated adverse event or any unresolved Grade $>$ 1 immune-mediated adverse event while receiving any previous immunotherapy agent other than immune checkpoint blockade agents
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation

N.4.2 Study Treatment

Study treatment in this arm will consist of atezolizumab in combination with tiragolumab, as determined by the investigator.

N.4.2.1 Formulation and Packaging

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.

Tiragolumab will be supplied by the Sponsor as a sterile liquid in a single-use, 15-mL glass vial. The vial contains approximately 10 mL (600 mg) of tiragolumab solution.

For further information on the formulation and handling of tiragolumab, please see the pharmacy manual and the Tiragolumab Investigator’s Brochure.

N.4.2.2 Dosage, Administration, and Compliance for Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor consultation, see Section 3.1.2 for treatment beyond disease progression). Atezolizumab should be administered prior to tiragolumab on days when both are administered.

If a delay in administration of either agent is necessary, reasonable effort should be made to keep the administration synced if clinically feasible (e.g., briefly delay administration of the other agent).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Administration of atezolizumab will be performed in a monitored setting where there is access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion [a] • 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. [a] • 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 measured within 60 minutes prior to the infusion. [a] • 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 clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. [a]

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Guidelines for medical management of infusion-related reactions (IRRs) are provided inSection N.5.2.2.7.

No dose reductions for atezolizumab are allowed. See Section N.5.2.1 and Section N.5.2.2 for management guidelines.

N.4.2.3 Dosage, Administration, and Compliance for Tiragolumab

Following the administration of atezolizumab and an observation period (see Table 1), patients will receive 600 mg tiragolumab at a fixed dose administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab dose is fixed and is not dependent on body weight.

Tiragolumab infusions will be administered per the instructions outlined in Table 2.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section N.5.2.1. Guidance on study drug administration in the context of management of specific adverse events is provided in Section N.5.2.2.

For further details on dose preparation, storage, and administration instructions for tiragolumab, refer to the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

Table 2 Administration of First and Subsequent Infusions of Tiragolumab

	Day 1, Cycle 1 Infusion	Day 1 Infusion of Subsequent Cycles
Infusion of tiragolumab	• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion.[a] • Tiragolumab should be infused over 60 (±15) minutes. • Vital signs should be recorded every 15 (±5) minutes during the infusion.[a]	• If the patient experienced an IRR during any previous infusion of tiragolumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent doses, at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the tiragolumab infusion.[a] • Tiragolumab 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. • Vital signs should be recorded during the infusion if clinically indicated.[a]
Observation period after infusion of tiragolumab	• After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of tiragolumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the patient experienced an infusion-associated adverse event in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of tiragolumab.[a] • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.

IRR = infusion-related reaction.

[a] Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

N.4.2.4 Guidelines for Administration of Atezolizumab in combination with Tiragolumab

The following rules apply as long as neither atezolizumab nor tiragolumab has been permanently discontinued:

- Treatment cycles will begin with dosing of atezolizumab followed by tiragolumab on Day 1 of each 21-day cycle. If either study drug is delayed for a related toxicity, it is recommended that the other study drug is also delayed because the safety profiles

for atezolizumab and tiragolumab are similar; however, a cycle may begin with the administration of atezolizumab as a single agent if considered appropriate at the discretion of the investigator, after consultation with the Medical Monitor.

- In case of delays in dosing of tiragolumab for study drug–related toxicity while atezolizumab is given as planned, it is recommended that the study drug being delayed will be administered at the next scheduled infusion (i.e., at the next scheduled 21-day cycle).

Guidelines for treatment interruption or discontinuation are provided in Section N.5.2.1 and Section N.5.2.2.

N.4.3 Concomitant Therapy

N.4.3.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- 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 N.4.3.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease (COPD) 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 may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment in consultation with the Medical Monitor. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

- 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 (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section N.4.3.2, Section N.4.3.3) 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 6).

N.4.3.2 Cautionary Therapy

N.4.3.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with tiragolumab and 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.

Patients with primary CNS tumors can be receiving concurrent treatment with corticosteroids in consultation with the Medical Monitor. Patients must be receiving a stable or decreasing dose for ≥5 days prior to the baseline magnetic resonance imaging (MRI) scan and at the time of drug initiation.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with tiragolumab and atezolizumab therapy (refer to Section N.5.2.1 and Section N.5.2.2 for details).

N.4.3.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

N.4.3.3 Prohibited Therapies

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 within 3 weeks prior to starting study treatment and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section N.4.3.1 for details).
- Investigational therapy 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 atezolizumab treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of study treatment.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with study treatment.

N.4.4 Arm-specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients receiving atezolizumab and tiragolumab. Refer to the schedule of activities (Section N.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (T4)
- HIV serology
- HBV serology, consisting of the following:
  - HBsAg, HBsAb, and total HBcAb for all patients
  - HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- EBV serology, including the following
  - EBV viral capsid antigen (VCA) immunoglobulin M (IgM)
  - EBV VCA immunoglobulin G (IgG) or Epstein-Barr nuclear antigen (EBNA) IgG
  - If clinically indicated: EBV PCR
- Urinalysis: pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted

- Coagulation test: INR and aPTT

Functional Assessments

- 12-lead electrocardiogram

N.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm N: atezolizumab plus tiragolumab.

N.5.1 Risks Associated with Study Treatment

N.5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome 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 Section N.5.2.2 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

N.5.1.2 Risks Associated with Tiragolumab

IRR *and immune-mediated hepatitis are* an identified risk of tiragolumab. *Additional immune-mediated adverse events, l*ymphopenia and embryofetal toxicity are potential risks with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of T-cell immunoreceptor with Ig and ITIM domains (TIGIT), tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Section N.5.2.2 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

N.5.1.3 Risks Associated with Combination Use of Tiragolumab and Atezolizumab

Based on results from nonclinical and/or clinical studies with each molecule as a single agent, clinical data with tiragolumab plus atezolizumab, there *are known and* potential overlapping *toxicities* in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive tumor cell (TC) immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, *additional* immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors (CPIs) to date has been incorporated into the design and safety management plan in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section N.4.1.2). Patients previously treated with approved or experimental cancer immunotherapy (CIT) will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Tiragolumab Investigator's Brochure), patients with active HIV, HBV, HCV, or EBV infections, known and/or suspected chronic active EBV infection, or tuberculosis and/or patients with recent severe infections will be excluded from this study (see Sections 4.1.2 and N.4.1.2).

N.5.2 Guidelines for Management of Adverse Events

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

N.5.2.1 Dose Modifications and Treatment Interruptions

No dose reductions for atezolizumab or tiragolumab are allowed. Interruptions to atezolizumab or tiragolumab treatment are described below (Section N.5.2.2).

N.5.2.2 Management of Specific Adverse Events Associated with Atezolizumab and Tiragolumab

Toxicities associated or possibly associated with atezolizumab *and/*or tiragolumab 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 *when clinically indicated*.

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 and/or tiragolumab 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.

- *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. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab and tiragolumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab and tiragolumab 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 and tiragolumab 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 and tiragolumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab and/or tiragolumab. *Resumption* of atezolizumab and/or tiragolumab may be considered *in patients who are* deriving benefit and has fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab and/or tiragolumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab and tiragolumab 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 the equivalent of ≤10 mg/day oral prednisone before atezolizumab and tiragolumab can be

resumed. If atezolizumab and tiragolumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab and tiragolumab. However, atezolizumab and tiragolumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab and tiragolumab 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 and tiragolumab 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 and tiragolumab 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.

N.5.2.2.1 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.

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. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 3.

Table 3 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue tiragolumab and atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab and tiragolumab.
Pulmonary event, Grade 2	• Withhold tiragolumab and 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and 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 tiragolumab and atezolizumab and contact 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 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.

BAL = bronchoscopic alveolar lavage.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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

N.5.2.2.2 Hepatic Events

Patients *eligible for study treatment* must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 4.

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

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

Table 4 Management Guidelines for Hepatic Events

Event	Management
Guidelines for patients without hepatocellular carcinoma	
Hepatic event, Grade 1	• Continue tiragolumab and atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 4 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for patients without hepatocellular carcinoma (cont.)	
Hepatic event, Grade 3 or 4	• Permanently discontinue tiragolumab and 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 Grade 1 or better, taper corticosteroids over ≥ 1 month.
Guidelines for patients with hepatocellular carcinoma	
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 tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on 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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 4 Management Guidelines for Hepatic Events (cont.)

Guidelines for patients with hepatocellular carcinoma (cont.)	
Event	Management
AST or ALT increases to >10×ULN or total bilirubin increases to >3×ULN	• Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 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.

LFT = liver function test; ULN = upper limit of normal.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.3 Gastrointestinal Events

Management guidelines for diarrhea or colitis are provided in Table 5.

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 5 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue tiragolumab and atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]

GI = gastrointestinal.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 5 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 3	• Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue tiragolumab and 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.4 Endocrine Events

Management guidelines for endocrine events are provided in Table 6.

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. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 6 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue tiragolumab and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding tiragolumab and atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume tirag*olumab and *atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold tiragolumab and 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 tiragolumab and atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]

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

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 6 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue tiragolumab and 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.
Grade 2 hyperthyroidism	• *Consider withholding tiragolumab and atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume tiragolumab and atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hyperthyroidism	• Withhold tiragolumab and atezolizumab. • Initiate treatment with anti-thyroid drug*s* such as methimazole or carbimazole as needed. • *Refer* to endocrinologist. • Resume tiragolumab and atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

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

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 6 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] • 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue tiragolumab and 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; TSH = thyroid-stimulating hormone.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 6 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 3 or 4	• Withhold tiragolumab and atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume tiragolumab and atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (panhypopituitarism), Grade 2 or 3	• Withhold tiragolumab and 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 if clinically indicated. • If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab permanently discontinue tiragolumab and atezolizumab *and contact the Medical Monitor.* [c] • For recurrent hypophysitis, treat as a Grade 4 event.

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

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 6 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (panhypopituitarism), Grade 4	• Permanently discontinue tiragolumab and 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 if clinically indicated.

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

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 7.

Table 7 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue tiragolumab and 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 tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue tiragolumab and atezolizumab and contact 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.6 *MANAGEMENT OF IMMUNE-MEDIATED CARDIAC EVENTS*

Management guidelines for cardiac events are provided in Table 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 8.

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 8. Withhold treatment with tiragolumab and atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 8 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue tiragolumab and 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.

N.5.2.2.7 *Infusion-Related Reactions*

No premedication is indicated for the administration of the Day 1, Cycle 1 infusion of tiragolumab or atezolizumab. However, patients who experience an infusion-related reaction (IRR) with the Day 1, Cycle 1 infusion of tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medication, 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 tiragolumab and atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of tiragolumab or atezolizumab administration and are generally mild to moderate in severity. Guidelines for medical management of IRRs during Cycle 1 are provided in Table 9. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 9 Management Guidelines for Infusion-Related Reactions

Event	*Management*
IRR, Grade 1	• *Reduce infusion rate to half the rate being given at the time of event onset.* • *After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.* • *If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.*
IRR, Grade 2	• *Interrupt infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs.*
IRR, Grade 3 or 4	• *Stop infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *Permanently discontinue tiragolumab or atezolizumab and contact the Medical Monitor.* [a]

IRR =infusion-related reaction.

[a] *Resumption of tiragolumab and 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 tiragolumab and 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.*

N.5.2.2.8 *Cytokine-Release Syndrome*

No premedication is indicated for the administration of Cycle 1 of tiragolumab or atezolizumab. However, patients who experience cytokine-release syndrome (CRS) with tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

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.

Guidelines for medical management of CRS are provided in Table 10.

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 10 Management Guidelines for 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 CRS.*
Grade 2 [a] *Fever* [b] *with at least one of the following:* • *Hypotension not requiring vasopressors* • *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 tiragolumab and atezolizumab, and contact the Medical Monitor.* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of tiragolumab and atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for CRS.* • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.*

Table 10 Management Guidelines for Cytokine-Release Syndrome (cont.)

Event	*Management*
Grade 3 [a] *Fever* [b] *with at least one of the following:* • *Hypotension requiring a vasopressor (with or without vasopressin)* • *Hypoxia requiring high-flow oxygen* [d] *by nasal cannula, face mask, non-rebreather mask, or Venturi mask*	• *Permanently discontinue tiragolumab and 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 at least one of the following:* • *Hypotension requiring multiple vasopressors (excluding vasopressin)* • *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• *Permanently discontinue tiragolumab and 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 10 Management Guidelines for 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; MAS =macrophage activation syndrome; NCCN =National Cancer Comprehensive Network; NCI =National Cancer Institute.

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 the ASTCT CRS consensus grading scale. NCI CTCAE v5.0 and the ASTCT CRS consensus grading scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine-Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

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

[c] *Symptomatic treatment may include oral or IV antihistamines, antipyretic 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 tiragolumab and 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 tiragolumab and atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for 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).*

N.5.2.2.9 Pancreatic Events

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 11.

Table 11 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue tiragolumab and atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 11 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to gastrointestinal 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.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.10 Dermatologic Events

The majority of cases of rash *reported with the use of atezolizumab and/or tiragolumab* were mild in severity and self-limiting, 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 12.

Table 12 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue tiragolumab and atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue tiragolumab and 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 tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 12 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	• Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold tiragolumab and 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 tiragolumab and atezolizumab.

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.11 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 13 *with specific guidelines for myelitis provided in Table 14*.

Table 13 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue tiragolumab and 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 tiragolumab and 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 tiragolumab and atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume tiragolumab and atezolizumab* [b] – *If event does not resolve fully while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue tiragolumab and 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 tiragolumab and atezolizumab and contact *the* Medical Monitor. [c] • 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 14 *Management Guidelines for Immune-Mediated Myelitis*

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue tiragolumab and atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue tiragolumab and 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 tiragolumab and atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

N.5.2.2.12 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is a potential risk with tiragolumab.

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 15.

Table 15 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue tiragolumab and 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.

N.5.2.2.13 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 16.

Table 16 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue tiragolumab and 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 tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue tiragolumab and 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.14 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 17.

Table 17 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue tiragolumab and atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact *the* Medical Monitor. [c]

[a] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab 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 17 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the. The Medical Monitor is available to advise as needed.

Table 17 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue tiragolumab and 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] Tiragolumab and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *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 tiragolumab and atezolizumab can be resumed.

[c] Resumption of tiragolumab and 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 and tiragolumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

N.5.2.2.15 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 $<100\times10^9$/L ($<100{,}000/\mu$L)
  - ANC $<1.0\times10^9$/L ($<1000/\mu$L)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (>500 ng/mL)
- Soluble 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 $\leq181\times10^9$/L ($\leq181{,}000/\mu$L)
  - 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 18.

Table 18 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue tiragolumab and 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.

N.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. In addition to the adverse events of special interest specified in Section 5.2.3, the following adverse events are required to be reported by the investigator immediately for patients receiving atezolizumab:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 × ULN

- Myositis
- Myopathies, including rhabdomyolysis
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- *Myelitis*
- *Facial paresis*

N.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤28 days *after* last study dose
Informed consent [d]	x			
Documentation of TMB-H/ MSI-H/dMMR status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
ECOG Performance Status [h]	x	x		x
Pregnancy test [i]	x	x		x
Chemistry [j]	x	x		x [c]
Hematology/CBC with differential [k]	x	x		x [c]
Coagulation panel [l]	x			x
HIV, HCV, HBV, EBV serology [m]	x			
Urinalysis [n]	x	x		x
ECG [o]	x	As clinically indicated		x
Thyroid function test (TSH, free T3 [or total T3], free T4) [p]	x	C1, D1 and every 4 cycles thereafter		x
Atezolizumab administration [q]		x		
Tiragolumab [r]		x		
Response Assessment [s, t]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [u]		Submit within 21 days of Cycle 1 Day 1		
Whole blood samples [v]	x		See footnote v	

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤28 days *after* last study dose
Adverse events [w]		Collected on an ongoing basis		*x* [w]
Concomitant medications [x]	x	Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; dMMR=deficient mismatch repair; EBNA=Epstein-Barr nuclear antigen; EBV=Epstein-Barr virus; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; Ig=immunoglobulin; IV = intravenous; LVEF = left ventricular ejection fraction; MSI-H=microsatellite-high; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PCR=polymerase chain reactionPD=progressive disease;; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; TMB-H=tumor mutational burden-high; TSH = thyroid-stimulating hormone; VCA=viral capsid antigen.

Note: Cycle=21 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC, chemistry panel, and thyroid function test are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post- chemotherapy discontinuation or 90 days post-atezolizumab discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of TMB-H/MSI-H/dMMR status should occur prior to performing other trial-related eligibility assessments. TMB-H should be determined using a tissue-based NGS assay.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[i] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[j] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[k] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[l] Coagulation includes aPTT and INR.

[m] All patients will be tested for HIV, HBV, HCV at screening. Patients with HBV or HIV will be exluded based on the criteria detailed in Section 4.1.2. Patients with HCV will be excluded based on the criteria in Section N.4.1.2. EBV serology samples will be collected at screening for the following: EBV VCA IgM, EBV VCA IgG or EBNA IgG. An EBV PCR test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV viral capsid antigen immunoglobulin M (IgM) test or positive EBV PCR test at screening are excluded. Additional EBV serology tests will be performed for patients who subsequently experience an acute inflammatory event, such as systemic inflammatory response syndrome, while receiving study treatment.

[n] Urinalysis consists of specific gravity, pH, glucose, protein, ketones, and blood.

[o] An ECG is required at screening, at the treatment discontinuation/completion visit, and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[p] TSH, free T3 (or total T3 at sites where free T3 is not performed), and free T4 will be collected at screening, on Day 1 of Cycles 1 and 4, every fourth cycle thereafter (e.g., Cycles 1, *5*, *9*, and *13, etc.*), and at the treatment discontinuation/completion visit.

[q] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Days 1 of each 21-day cycle. The initial infusion 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.

[r] Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Days 1 of each 21-day cycle. The initial dose will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Dosing of both study drugs will occur only if the clinical assessment and local laboratory test results are acceptable. If a tumor assessment was performed, results must be reviewed by the investigator before dosing of study treatment.

[s] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[t] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors) or loss of clinical benefit (with Medical Monitor consultation; see Section 3.1.2), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[u] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue are available, the recent tissue should be preferentially submitted.

[v] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of chemotherapy or 90 days after the final dose of atezolizumab, whichever is longer. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-chemotherapy discontinuation or 90 days post-atezolizumab discontinuation, whichever is longer. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[x] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study treatment.

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Appendix 24
Arm O: Pralsetinib in Patients with RET Fusion-Positive Tumors

25. ARM O: PRALSETINIB IN PATIENTS WITH RET FUSION-POSITIVE TUMORS

TABLE OF CONTENTS

O.4 MATERIALS AND METHODS

O.4.1 PATIENTS

To be enrolled in Arm O: pralsetinib treatment, patients must have met and continue to meet all general eligibility criteria (see Section 4.1), in addition to the arm-specific criteria below.

O.4.1.1 Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm O: pralsetinib treatment:

- RET fusion positivity, except patients with non-small cell lung cancer (NSCLC) or thyroid cancers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' RET fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Ability to swallow pralsetinib intact, without chewing, crushing, or opening the capsules/tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined non-hormonal contraception methods that result in a failure rate of $<$1% per year during the treatment period and for at least 14 days after the last dose of pralsetinib; and agreement to refrain from donating eggs during this same period. See Appendix 2 for details on contraception requirements.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$1% per year during the treatment period and for at least 7 days after the last dose of pralsetinib, and agreement to refrain from donating sperm during this same period. See Appendix 2 for details on contraception requirements.

O.4.1.2 Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm O: pralsetinib treatment:

- RET fusion-positive NSCLC
- RET fusion-positive thyroid cancer
- Patient's tumor has any additional known primary driver alterations other than RET, such as targetable mutations of EGFR, ALK, ROS1, MET, KRAS or BRAF.
- Known history of hypersensitivity to pralsetinib or any of its excipients
- Prior treatment with RET inhibitors (approved or investigational)

Note: Other prior anti-cancer therapy is allowed

- Screening QT interval corrected using Fridericia's formula (QTcF) $>$480 milliseconds, history of prolonged QT syndrome or torsades de pointes, and/or familial history of prolonged QT syndrome
- History of pneumonitis during the prior 12 months
- Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids $>$10 mg/day of prednisone (or equivalent)
- Active, uncontrolled infection (viral, bacterial, or fungal)
  - Participants with controlled infections who are stable on treatment may be eligible if the benefit–risk assessment is justified
- Clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
- Neutrophil growth factor support within 14 days of the first dose of study drug
- Treatment with a prohibited medication or herbal remedy that cannot be discontinued at least 14 days before the start of study drug administration.

O.4.2 STUDY TREATMENT

Study treatment in this arm will consist of pralsetinib.

O.4.2.1 Formulation and Packaging

Pralsetinib will be supplied by the Sponsor as 100-mg capsules.

The study drug will be periodically tested and monitored for its acceptable shelf life. Any study drug that fails to comply with the manufactured specifications will be promptly removed from the clinical trial site and replaced with new supplies by the Sponsor (or designee).

Each bottle will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The investigator should ensure that the study drug is stored in appropriate conditions in a secure location with controlled access. For information on the packaging, handling, and storage, see the Pharmacy Manual and Pralsetinib Investigator's Brochure.

O.4.2.2 Dosage, Administration, and Compliance

Study treatment will be administered in 28-day cycles.

Pralsetinib will be self-administered by patients orally at home (except on clinic days Section O.6), at the same time each day, on a starting dose of 400 mg/day (four 100-mg

capsules per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

Pralsetinib should be taken in the morning with a glass of water in a fasted state, with no food intake beginning 2 hours before until 1 hour after study drug administration. The capsules should not be opened and the contents of the capsules should not be dissolved.

A missed dose can be taken within 12 hours of the scheduled time. After that, patients should take the next dose the following day, without compensating for the missed dose (including vomited doses).

Guidelines for pralsetinib dosage modification and treatment interruption or discontinuation are provided in Section O.5.2.1.

See Section 4.3.2 for details on assessment of compliance for self-administered oral study drugs.

Accidental overdose or medication errors 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 also be reported as described in Section 5.3.5.12.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

O.4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions

O.4.3.1 Permitted Therapy

Anti-emetic and anti-diarrheal treatments may be used at the investigator's discretion (in accordance with the local guidelines) after documented nausea, vomiting, or diarrhea has occurred in patients who are not taking medications to manage these symptoms. Prophylaxis for nausea, vomiting, or diarrhea may be instituted beginning on Cycle 2 Day 1 in patients who experience these toxicities during Cycle 1, and during Cycle 1 for patients who experience nausea, vomiting or diarrhea.

In certain instances, palliative radiotherapy to specific sites is permitted if considered medically necessary by the investigator. The Sponsor must be notified if palliative radiotherapy is started; however, the need for radiotherapy will generally be considered indicative of progressive disease.

If palliative radiation is indicated for bone lesions, palliative radiation may start within 24 hours of the last dose of pralsetinib, unless, in the judgment of the investigator, patient safety will require a longer washout period prior to palliative therapy. Dosing of pralsetinib may resume with the resolution of any radiation toxicity to Grade 1 or better.

If radiation therapy or surgical excision of target lesion is determined to be in patient's best interest and cannot be avoided, the Medical Monitor should be consulted. Note that radiation or surgical excision of target lesions may render patients unevaluable for further response assessments.

O.4.3.2 Concomitant Therapy to Be Used With Caution

The following medications are to be used with caution during the study.

- In vitro metabolism studies in human liver microsomes have demonstrated that pralsetinib is a direct moderate inhibitor and inducer of multiple P450 enzymes (CYP2C8, CYP3A4, and CYP2C9). Pralsetinib is also a time-dependent inhibitor of CYP3A4/5.
- Pralsetinib is an inhibitor of P-glycoprotein (P-gp), BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K at clinically relevant concentrations. In patients, pralsetinib may alter or increase the plasma concentration of co-administered sensitive CYP2C8, CYP3A4, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K substrates.
- Medications that are sensitive CYP2C8, CYP3A4, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K substrates with known drug–drug interaction potential should be used with caution.
- Lists of relevant drugs to be used with caution are provided in Appendix 7.

O.4.3.3 Prohibited Therapy

- In vitro metabolism studies indicate that pralsetinib oxidation is primarily mediated by CYP3A4 and to a lesser extent by CYP2D6 and CYP2C9, and glucuronidation by UGT1A4. As a precaution, strong inhibitors as well as inducers of CYP3A4 are prohibited. Drug transporter studies in cells overexpressing P-gp indicate that pralsetinib is likely also a P-gp substrate. Medications that are strong dual inhibitors of P-gp and CYP3A4 are prohibited.
  - Refer to Appendix 7 for a list of relevant prohibited medications.
- Any investigational agent or device other than pralsetinib, including commercially available agents that are investigational for the treatment of the patient's underlying malignancy.
- Any anti-cancer treatment other than study drug.
- Use of herbal medications (e.g., St. John's Wort) should be avoided when possible.

O.4.3.4 Prohibited Food

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit should be avoided for up to 14 days prior to and during the treatment period.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period.

O.4.4 Pralsetinib-Specific Assessments

In addition to the study assessments described in Section 4.5, the following assessments are required for patients in the pralsetinib treatment arm. Refer to the schedule of activities (Section O.6) for arm-specific assessment timepoints.

Local Laboratory Assessments

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

- Coagulation: INR and aPTT
- Urinalysis (dipstick): (pH, specific gravity, glucose, protein, ketones, blood, nitrite, leukocyte esterase [or white blood cells]). Note that for sites that do not routinely perform leukocyte esterase in the urinalysis (dipstick) test, white blood cell result in the report of urinalysis with dry chemistry (dipstick) method is acceptable.

Other Assessments

- Vital signs will include measurements of pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- Single 12-lead ECG

O.5 SAFETY PLAN

Please refer to Section 5 for general instructions with regard to the assessment of safety in this study. Following are further instructions specific to Arm O: pralsetinib treatment.

O.5.1 Risks Associated with Pralsetinib

Pralsetinib has been associated with risks such as the following: pneumonitis, pneumonia/lung infections, tumor lysis syndrome, hypertension and hepatotoxicity. Refer to the Pralsetinib Investigator's Brochure for a detailed description of anticipated safety risks for pralsetinib.

O.5.2 Management of Patients Who Experience Adverse Events with Pralsetinib

Guidelines for management of specific adverse events and dose modification or interruption are outlined below. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases.

O.5.2.1 Dose Modifications and Interruptions

Adverse events associated with pralsetinib can often be managed with concomitant medications, supportive care (see Section O.4.3.1 and Section O.5.2.2), and/or dose modifications as per Table 1 and Table 2.

The dose of pralsetinib can be reduced in decrements of 100 mg and no more than 3 dose reductions will be allowed. Pralsetinib dose reductions to below 100 mg QD are not permitted. If a patient requires dose reduction below 100 mg QD, study treatment should be discontinued.

The possible daily doses of pralsetinib are shown in Table 1.

Table 1 Pralsetinib Dose Reductions

Dose Level	Pralsetinib
Starting dose	400 mg QD
First dose reduction	300 mg QD
Second dose reduction	200 mg QD
Third dose reduction	100 mg QD
Fourth dose reduction	Not permitted

QD = once a day.

Pralsetinib treatment may be interrupted for a maximum of 56 days (8 weeks) to allow for sufficient recovery from any toxicity if a patient is still deriving clinical benefit in the judgment of the investigator. In general, if a toxicity that is considered to be related to the study drug does not resolve to ≤ Grade 1 or has not returned to baseline after dose interruption for more than 56 days, the patient should be discontinued from study treatment unless a specific exception is made following discussion with the Medical Monitor because resumption of treatment is considered to be in the best interest of the patient, and this is documented in writing. Additionally, the Medical Monitor must be informed if an adverse event that is not considered to be related to the study treatment requires a dose interruption for more than 56 days.

Pralsetinib may be suspended for reasons other than toxicity (eg, surgical procedures), however pralsetinib should be interrupted at least 5 days in advance of surgery and resumed 2 weeks after major surgery and until adequate wound healing. If there are questions regarding whether or not study drug should be interrupted, the investigator should consult with the Medical Monitor.

Table 2 Dose Modification and Interruptions for Pralsetinib Related Adverse Events

Adverse Drug Reaction	Severity [a]	Dose Modification
Non-Hematologic Toxicity [b]	Grade 1	• No dose interruption or modification required
	Grade 2	• No dose interruption or modification required. If dose interruption is necessary, on improvement resume dosing without dose reduction
	Grade 3	• Occurrence at 200–400 mg dose: Hold until event is ≤ Grade 2, or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose • Occurrence at 100 mg dose: Discontinue pralsetinib
	Grade 4	• Discontinue pralsetinib unless resumption of dosing is approved by the medical monitor.
Hematologic Toxicity: Anemia, Neutropenia, Thrombocytopenia	Grade 1 or Grade 2	• No dose interruption or modification required
	Grade 3 or Grade 4	• Occurrence at 200–400 mg dose: Hold until event is ≤ Grade 2, or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose • Occurrence at 100 mg: Discontinue pralsetinib
Hematologic Toxicity: Lymphopenia	Grade 1 or Grade 2	• No dose interruption or modification required
	Grade 3	• Occurrence at 200–400 mg dose: Reduce the dose by 100 mg less than the current dose. Interruption of dosing can be done based on clinical circumstances but is not required • Occurrence at 100 mg: Discontinue pralsetinib
	Grade 4	• Occurrence at 200–400 mg dose: Hold until event is ≤ Grade 3, or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose • Occurrence at 100 mg: Discontinue pralsetinib

AE = adverse event; NCI CTCAE v5 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5

[a] According to NCI CTCAE v5.0

[b] Except for selected AEs: See specific advice for pneumonitis and hypertension.

O.5.2.2 Guidelines for Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in the subsections below.

O.5.2.2.1 Pneumonia/Lung Infections

The diagnosis of pneumonia and lung infections (including opportunistic infections), some of which have been fatal, have been reported with patients treated with pralsetinib. The determination of causal relationship to the drug is often confounded by immunosuppression related to the patient's underlying disease, prior therapy (such as immunotherapy and steroids), and other risk factors for infection such as myelosuppression. Pneumonias and other lung infections should be managed with systemic antibiotics and other supportive management.

If the causality is at least possibly related to the study drug, dose interruption and potential dose reduction and/or discontinuation should follow the guidelines in Table 2 , dose modification for non-hematologic toxicity.

O.5.2.2.2 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been observed following pralsetinib treatment. Investigators should monitor electrolyte status and renal function via laboratory testing. Patients with TLS may require supportive care with intravenous fluids and correction of electrolyte imbalances.

Patients who are at risk for TLS at study entry, such as those with high tumor burden, should be well hydrated before initiation of pralsetinib and avoid dehydration during the first cycle. If TLS is suspected, investigators should manage the adverse event(s) according to standard institutional practices or accepted oncology management guidelines (Coiffier et al. 2008; Klastersky et al. 2016).

O.5.2.2.3 Hypertension

Treat with standard of care antihypertensive therapy. Dose modification is not required if hypertension can be managed with supportive medications. If dose modification is necessary, please use dose modification guidelines for non-hematologic toxicity (Table 2).

O.5.2.2.4 Hepatotoxicity

Serious hepatic adverse reactions have been observed with pralsetinib. Pralsetinib treatment must be discontinued permanently if either of the following occurs:

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

O.5.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Section 5.2.3 describes adverse events of special interest that are required to be reported by the Investigator to the Sponsor immediately for all study treatments, and Section 5.4.2 provides reporting instructions. There are no additional adverse events of special interest for the RET fusion-positive cohort other than those specified in Section 5.2.3.

O.5.4 Selected Adverse Events

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

- Pneumonitis
- Pneumonia
- Hepatotoxicity
- Hypertension
- Hemorrhagic events
- Tumor lysis syndrome

O.6 SCHEDULE OF ACTIVITIES

Assessments	Pre-treatment Screening	Treatment Period		End of Treatment Visit [b]
Day and Study Cycle		Day 1 of Each Cycle	Other Days as Specified	
(Window)	–28 to –1 [a]	(±3)	(±3)	≤ 28 days *after* last study dose
Informed consent [d]	x			
Documentation of positive RET fusion status by local test [e]	x			
Medical history and baseline conditions [f]	x			
Physical Examination [g]	x	As clinically indicated		
Vital signs	x	x	x [h]	
ECOG Performance Status [i]	x	x		x
Pregnancy test [j]	x	x		x
Chemistry [k]	x	x	x [k]	x [c]
Hematology/CBC with differential [l]	x	x		x [c]
Coagulation panel [m]	x			
Urinalysis [n]	x	x		x
12-lead ECG [o]	x	D1 of each cycle and as clinically indicated		x
Response assessment [p, q]	x	Every 8 (±1) weeks for 3 evaluations, then every 12 (±2) weeks		
Pre-treatment tumor tissue sample for central testing (if applicable) [r]		Submit within 21 days of Cycle 1 Day 1		
Whole blood samples [s]	x		see footnote s	
Pralsetinib compliance assessment [t]		x		x
Pralsetinib dispensing		x		
Adverse events [u]		Collected on an ongoing basis		*x* [u]
Concomitant medications [v]		Collected on an ongoing basis		

AE=adverse event; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computerized tomography; ctDNA=circulating tumor DNA; D=day; ECG=electrocardiogram; ECHO = echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic Case Report Form; FMI=Foundation Medicine, Inc.; ICF=informed consent form; IV = intravenous; LVEF = left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA = multiple-gated acquisition; PD=progressive disease; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event.

Note: Cycle=28 days.

[a] The medical history, ECOG PS, hematology/CBC, and chemistry panel should be done ≤ 28 days prior to initiation of treatment. However, if the hematology/CBC and chemistry panel are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 28 days after the last dose of study treatment for end-of-treatment follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. If the patient's worsening disease combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

[c] *If the hematology/CBC and chemistry panel are obtained within 7 days prior to treatment discontinuation, they do not have to be repeated unless clinically indicated.*

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Confirmation of positive RET fusion status should occur prior to performing other trial-related eligibility assessments.

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

[g] A complete physical examination, performed at screening should include height, weight, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed 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.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Vital signs should be assessed at screening and day 1 of each cycle. Additionally, blood pressure should be assessed at C1D8.

[i] All performance status will be assessed according to ECOG PS definitions provided in Appendix 5. It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

[j] Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must

be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug.

[k] Will include measurements of glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, total protein, and albumin. Screening results must be reviewed and documented prior to administration of the first dose of study treatment. If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1. Subsequent chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before). AST and ALT should also be assessed on D15 of cycles 1-3.

[l] Hematology/CBC with differential includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If results are obtained within 7 days of Cycle 1, Day 1 they do not have to be repeated on Cycle 1 Day 1.

[m] Coagulation includes aPTT and INR.

[n] Urinalysis (dipstick): (pH, specific gravity, glucose, protein, ketones, blood, nitrite, leukocyte esterase [or white blood cells]). Note that for sites that do not routinely perform leukocyte esterase in the urinalysis (dipstick) test, white blood cell result in the report of urinalysis with dry chemistry (dipstick) method is acceptable.

[o] A single 12-lead ECG should be performed during screening, on Day 1 of every treatment cycle, at the end of treatment, and as clinically indicated. 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. If at a particular post-dose timepoint (if applicable) the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the Investigator.

[p] All known sites of disease must be assessed and documented at screening and reassessed at each subsequent tumor evaluation. 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. 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 of the abdomen, pelvis, and head should be performed. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[q] At each subsequent tumor assessment, all measurable and evaluable lesions should be re-assessed using the same radiographic procedures every 8 ($\pm$1) weeks for 3 evaluations, then every 12 ($\pm$2) weeks thereafter regardless of dose delays or treatment discontinuation, until investigator-determined radiographic disease progression per RECIST v1.1 or RANO (for primary CNS tumors), withdrawal of consent, termination of an individual study arm by the Sponsor, or death, whichever occurs first.

[r] For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

[s] Blood samples will be collected at screening, 8 weeks after first treatment (or within one week of the first tumor assessment), and at tumor progression *(within 7 days after progression)* for analyses including ctDNA.

[t] Pralsetinib will be self-administered by patients orally at home (except on clinic days, Section O.4.2.2), at the same time each day, on a starting dose of 400 mg/day (four 100 mg capsules per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. Compliance will be reviewed with the patient prior to starting each cycle.

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All patients will be followed until treatment-related toxicities resolve or for at least 28 days post-study drug discontinuation. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[v] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the final dose of study drug.

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