A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 2 Study of Atezolizumab With or Without Entinostat in Patients with Advanced Triple Negative Breast Cancer, with a Phase 1b Lead in Phase [SNDX-275-0602]

Syndax Protocol SNDX-275-0602

TRIO Study Number: TRIO025

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Date, Version:	11 Sep 2018, Version 3.0
Amendment:	2
IND Number:	64,722

Investigator's Agreement

I have read the attached protocol entitled **"A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 2 Study of Atezolizumab With or Without Entinostat in Patients with Advanced Triple Negative Breast Cancer, with a Phase 1b Lead in Phase [SNDX-275-0602]**", dated 11 Sep 2018 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice applicable regulations of the Food and Drug Administration and other applicable regulations.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me
- my sub-investigators

at the start of the study, at study completion, and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Syndax.

Signature

Name of Principal Investigator Date

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1.PROTOCOL SYNOPSIS SNDX-275-0602 (TRIO-025)

Title: A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 2 Study of Atezolizumab With or Without Entinostat in Patients with Advanced Triple Negative Breast Cancer, with a Phase 1b Lead in Phase [SNDX-275-0602 (TRIO025)]

Study Phase: Phase 1b/2

Indication: Advanced Triple Negative Breast Cancer (aTNBC)

Primary Objective:

Phase 1b: (Dose Determination Cohort): To determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of entinostat (SNDX-275) given in combination with atezolizumab.

Phase 2 (Expansion Cohort): To perform an evaluation of the efficacy of entinostat at the RP2D in combination with atezolizumab in patients with aTNBC, as determined by the duration of progression-free survival (PFS) based on the local investigator's assessment of progressive disease Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Objectives:

Efficacy: To evaluate the efficacy of entinostat in combination with atezolizumab in patients with aTNBC, as determined by:

- PFS based on immune response RECIST (irRECIST)
- Overall response rate (ORR) (i.e., complete response [CR] or partial response [PR]) based on RECIST 1.1
- Overall response rate (ORR) (i.e., complete response [CR] or partial response [PR]) based on irRECIST
- Clinical benefit rate (CBR) (i.e. CR or PR or stable disease [SD] for at least 24 weeks) based on RECIST 1.1 and irRECIST
- Overall survival (OS)

In patients with best overall response of CR or PR:

- Duration of response (DOR)
- Time to response (TTR)

Safety: To evaluate safety and the tolerability of entinostat in combination with atezolizumab, as measured by clinical adverse events (AEs) and laboratory parameters.

Exploratory Objectives:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Exploratory Objectives cont'd

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Hypothesis:

Phase 1b: The combination of atezolizumab and entinostat at a biologically active dose will be sufficiently safe and well tolerated to warrant further investigation.

Phase 2: Entinostat at the dose determined in Phase 1b combined with atezolizumab will result in an improved progression free survival compared to atezolizumab alone.

Study Design:

This is a Phase 1b/2 study evaluating the combination of entinostat plus atezolizumab in patients with aTNBC. The study has 2 phases: an open-label Dose Determination Phase (Phase 1b) followed by an Expansion Phase (Phase 2). The Expansion Phase will evaluate the efficacy and safety of entinostat when administered at the RP2D with atezolizumab in patients with aTNBC in a randomized, double-blind, placebo-controlled setting. Following the enrollment and completion of Cycle 1 of the first 20 patients in the Expansion Phase, cumulative study safety data will be reviewed by an independent safety review board. Up to 88 evaluable patients are anticipated if the study completes all phases of evaluation (up to 18 patients for Phase 1b, up to 70 patients for Phase 2). Up to 50 international study centers may participate.

Regardless of phase, patients will be screened for study eligibility within 21 days before enrollment into the study. Patients who are determined to be eligible based on screening assessments will be enrolled in the study within 3 business days of starting study treatment Cycle 1, Day 1 (C1D1).

A treatment cycle is 3 weeks (21 days) in length. The dose of atezolizumab will be fixed at 1200 mg IV q 3 weeks (day 1 of each cycle) for all patients. Entinostat (during the Phase 1b Dose Determination Phase) and entinostat / placebo (during Phase 2, Expansion Phase) will be administered orally on days 1, 8 and 15 of each 21 day cycle. The Dose Determination Phase will begin with a starting dose (dose level 1) of entinostat 5 mg po weekly. If dose level 1 exceeds the MTD, then entinostat 3 mg po weekly (dose level -1) will be investigated. If dose level -1 exceeds the MTD, then entinostat 2 mg po weekly (dose level -2) will be investigated. Dosing is planned to be continuous unless interrupted for management of an adverse event. The entinostat dose determined appropriate for combination with atezolizumab will then be taken forward into the Phase 2 Expansion Phase of the study as the RP2D.

During treatment, patients will attend study center visits and have study evaluations performed on C1D1, C1D8, and C1D15; D1 and D15 of C2; and on D1 of each cycle thereafter. Patients will have radiological disease assessments performed within 28 days prior to the first dose of study drug, and then every 6 weeks (+/-3 days) through week 36 (Weeks 6, 12, 18, 24, 30, 36) until unequivocal progressive disease. Patients remaining on study after week 36 will undergo radiological disease assessments every 9 weeks (+/- 3 days) until unequivocal progressive disease occurs. Disease will be assessed by computed tomography (CT), magnetic resonance imaging (MRI), and bone scans, as appropriate using the same method as used for the screening evaluation, and response will be assessed by the Investigator using RECIST 1.1.

Safety will be assessed during the study by documentation of AEs using United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, clinical laboratory tests, physical examinations, vital sign measurements, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance status. Adverse events of special interest (AESI) will be collected and reviewed in a manner consistent with serious adverse event reporting procedures.

Fresh tumor tissue core biopsy samples will be collected during the study as follows:

- During screening from all patients on a mandatory basis. Archival biopsies when available will also be collected for comparison.
- On C2D15 (+3 days) on an optional basis from patients in the Dose Determination Phase. All patients will be encouraged to provide an optional biopsy in order to help understand dose-immune correlate effects.
- On C2D15 (+3 days) on a mandatory basis until 20 samples are obtained in the Phase 2 portion and on an optional basis for subsequent patients in this phase 2 expansion.
- At the end of study treatment prior to the start of another systemic therapy, on an optional basis.
- At the time of disease progression on an optional basis.
- If, based on an interim review of tumor tissue data from the initial patients in the Phase 2 portion such data are considered informative, then tumor tissue samples may be collected on a mandatory basis from all subsequent patients on C2D15 (+3 days). Alternatively, if such data are not considered informative, these samples will not be collected from subsequent patients.

Blood for immune correlates is to be collected pre-dose on C1D1, C2D1, C2D15 and C3D1 and at the end of treatment visit. Blood for protein lysine acetylation testing will be collected pre-dose on C1D1 and C1D15.

Blood samples for determination of entinostat levels will be collected pre-dose on C1D1 and 2-4 hours post dose; anytime post dose on C1D8 and D15, and pre-dose on C2D1.

Blood samples for determination of atezolizumab levels and anti-atezolizumab antibodies will be collected pre-dose on C1D1 and again 30 minutes (+/- 10 minutes) following infusion completion (this sample is for PK only), and pre-dose on C2D1, C4D1 and at the end of treatment visit. A PK sample will also be collected from any patient who continues to be followed per protocol for PFS, 120 days after the end of treatment visit.

Patients will remain on study treatment until unequivocal progression of disease (PD), intolerable toxicity, or one of the other study withdrawal criteria is met (Protocol Section 11). Patients with radiographic progression only, as defined by RECIST 1.1 should continue on study treatment until unequivocal progressive disease is determined as defined by irRECIST, at the discretion of the investigator. After study treatment discontinuation, patients will complete an End of Treatment (EOT) visit within 7 days after the last study drug dose and a Safety Follow-up (F/U) visit 30 days (+/-3 days) later. After completion of the 30-day (+/- 3 days) Safety F/U visit, patients who have not experienced PD, are to be followed every 6 weeks for a clinic visit and radiological imaging until unequivocal progressive disease or until study week 36, whichever occurs first. If PD has not been documented at that time, patients will be followed every 9 weeks for radiological imaging until unequivocal progressive disease, death or end of the study whichever occurs first. Patients who discontinue study treatment for PD will be contacted every 3 months for survival status and post study therapies until death or closure of the study by the Sponsor.

Phase 1b / Dose Determination Phase: Up to 18 patients are expected to be enrolled in the Dose Determination Phase of the study which employs a classical 3+3 design, with the determination of DLT and the MTD and/or RP2D based on entinostat in combination with atezolizumab in C1. All dose cohorts will receive entinostat orally at the assigned dose on Days 1, 8 and 15 along with atezolizumab 1200 mg on Day 1 of a 21 day cycle. Dose group 1 will include 3-6 patients who will receive entinostat at a starting dose of 5 mg. If the entinostat 5 mg dose exceeds the MTD, then a 3 mg dose of entinostat (Dose Group

-1) will be evaluated in the same manner. If the entinostat 3 mg dose exceeds the MTD, then a 2 mg dose of entinostat (Dose Group -2) will be evaluated in the same manner. All patients within a cohort are to complete C1, have safety assessments performed through C2D1, and be assessed for DLT before enrollment of additional patients may commence. If <33% patients within a cohort have a DLT (i.e., <2 of 6), then enrollment of the Phase 2 Expansion cohort may commence with approval from the Syndax Study Physician.

If the -2 dose level exceeds the MTD, then the study will discontinue or additional doses or dosing schedules may be investigated via a protocol amendment. Also, based on evaluation of the safety and tolerability data gathered during the dose determination phase together with data from other clinical trials, it may also be decided that accrual will take place at an alternate dose level or dosing schedule via a protocol amendment.

Toxicities will be assessed by the Investigator using the United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Although decisions regarding subsequent patient dosing will be made based on review of data from C1, safety data will also be collected from all patients continuing treatment and these data will be reviewed in an ongoing manner by the Syndax Study Physician in consultation with the Investigators. Any detected cumulative toxicity may require later dose reductions and/or other changes to the dosing schedule, as appropriate, including further refinement of the RP2D.

Phase 2 / Expansion: In the Expansion Phase, the efficacy and safety of entinostat (compared to placebo) in combination with atezolizumab will be evaluated using the RP2D identified in the Dose Determination Phase. Following the enrollment and completion through Cycle 1 of the first 20 patients in the Expansion Phase, cumulative study safety data will be reviewed by a Data Safety Monitoring Board. Up to 70 patients with aTNBC will be randomized to receive atezolizumab + entinostat or atezolizumab + placebo in a 1:1 ratio.

Sample Size Considerations

Dose Determination Phase

Three to 6 patients will be enrolled in each dose cohort based on a standard Phase 1 dose scheme. Each patient will be counted in only 1 dose cohort. Six patients will need to be treated in a dose level for it to be considered MTD or the RP2D. The total number of patients to be enrolled in the Dose Determination Phase will be determined by the number of necessary dose cohorts required to achieve the MTD or RP2D.

A starting sample size of at least 3 patients per dose cohort, expanding to 6 patients in the event of a marginal DLT rate (33%) was deemed to be a safe and conventional approach in the dose confirmation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 83% chance that dose escalation would be halted in a given cohort.

Note: Patients who discontinued the study for reasons other than study drug related toxicities before completing C1 may be replaced.

Expansion Phase: Phase 2 aTNBC Cohort

The Expansion Phase will evaluate the efficacy and safety of entinostat (compared to placebo) when administered at the RP2D with atezolizumab in a randomized, double-blind, placebo-controlled setting. PFS will be the primary measure of efficacy; secondary measures of efficacy include ORR, CBR, DOR, TTR, and OS. Up to 70 eligible patients with aTNBC will be randomized to receive atezolizumab with entinostat or placebo in a 1:1 allocation. The sample size was determined based on the following considerations: True median PFS for patients with a TNBC receiving atezolizumab monotherapy is expected to be approximately 4 months when measured from randomization. It is hypothesized the combination of entinostat and atezolizumab will improve true median PFS by 3 months (i.e., median PFS of 4 vs. 7 months). Under the exponential distribution, such an improvement in median PFS represents a reduction of 43% for the true PFS failure hazard rate or equivalently, a hazard ratio of 0.57. The primary

analysis of PFS will be performed using a stratified log-rank test, stratifying on the randomization stratification factor of geographic location. Total information of 60 PFS failures, defined as documented progressive disease by RECIST 1.1 or death due to any cause without documented progressive disease beforehand, is estimated to provide 80% power to detect the aforementioned 43% reduction in the PFS failure hazard rate with one-sided significance level of 0.1. Assuming approximately 9 months of accrual and an additional 9 months of follow-up, total accrual of 70 patients (approximately 35 per treatment arm) is projected to result in 60 PFS failures within approximately 18 months of the date the first patient is randomized. Patients who discontinue study treatment for reasons not due to documented progressive disease by RECIST 1.1 will continue to undergo disease assessments until the earlier of documented progressive disease, death, or withdrawal of consent/lost to follow-up. It is anticipated that the number of patients who will drop out of the study without PFS failure beforehand will be low (expected to not exceed 2–3%). Depending on the actual number of such dropouts, the number of patients accrued may be increased by 6–10 additional patients to accommodate for a higher-than-expected number of dropouts.

The sample size and number of PFS failures was adjusted using the O'Brien-Fleming group sequential procedure to account for one planned interim analysis of PFS after 45 events (75% information). It is projected 75% and 100% of total information will be reported at approximately 12 and 18 months, respectively. The interim analysis will be performed to support the Sponsor's product development plans and ongoing resourcing activities. Although there are no plans to terminate the study early because of early evidence of superior efficacy for the combination treatment, the significance levels at the interim analysis and final analysis will be adjusted to maintain control of the overall type I error rate for multiple testing of PFS (O'Brien 1979).

Endpoints

Primary Efficacy Endpoint:

- PFS, as determined by the local investigator using RECIST 1.1

Secondary Endpoints: (analyzed in the same populations as the primary endpoint):

- PFS by immune response RECIST (irRECIST)
- ORR (CR or PR) by RECIST 1.1 and irRECIST
- CBR (CR, PR, or SD for at least 24 weeks)
- OS

In patients who experience best overall response of CR or PR:

- DOR
- TTR

Safety:

- Determination of DLT, MTD and RP2D
- AEs
- Clinical laboratory parameters, vital signs, physical exam

Exploratory:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Summary of Patient Eligibility Criteria:

Inclusion Criteria

Patients meeting all of the following criteria are considered eligible to participate in the study:

1. Females aged 18 years or older on the day written informed consent is given.
2. Has histologically or cytologically confirmed triple negative breast adenocarcinomathat is either metastatic (stage IV of the TNM classification) or locally recurrent and not amenable to local curative treatment. TNBC diagnosis should be based on local ER/PgR/HER-2 laboratory results and will be defined as HER2 negativity (IHC 0-1 and/or ISH non-amplification) and ER and PgR negativity (<1%). Disease must also be amenable to a core biopsy (image-guided if applicable) at screening and for certain cohorts as described in the protocol, at least once during study treatment.
3. Evidence of measurable (according to RECIST version 1.1) locally recurrent or metastatic disease based on imaging studies (e.g., CT, MRI) within 28 days before the first dose of study drug.
4. Has received at least 1, but no more than 2, prior lines of systemic therapy for locally recurrent and/or metastatic disease.
5. If patient has a history of treated asymptomatic CNS metastases they are eligible, provided they meet all of the following criteria:
    - Patient has measurable disease outside CNS;
    - Patient does not have metastases to midbrain, pons, medulla or spinal cord;
    - Patient is not on corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed);
    - Patient has not had whole-brain radiation within 6 weeks prior to study enrollment;
    - Patient has stable CNS disease as demonstrated by at least 4 weeks of stability between the last intervention scan and the study screening scan
6. ECOG performance status of 0 or 1.
7. Has the following laboratory parameters within 21 days before enrollment

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L

System	Laboratory Value
Renal	
Creatinine **OR**	≤1.5× the upper limit of normal (ULN) **OR**
Measured or calculated[1] creatinine clearance (CrCl) (glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≥60 mL/min for patient with creatinine levels >1.5× institutional ULN
Hepatic	
Total bilirubin	≤1.5×ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5×ULN
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5×ULN **OR** ≤5×ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[1] Creatinine clearance should be calculated per institutional standard.

8. If a female of childbearing potential, has a negative serum blood pregnancy test during screening and a negative urine pregnancy test within 3 days prior to receiving the first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a urine test is not required. Note: Women of childbearing potential (WoCP) are any women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation. Menopause is defined as at least 12 consecutive months since date of last menstruation, FSH and estradiol in postmenopausal ranges. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. WoCP include women who have experienced menopause onset < 12 months prior to enrollment.
9. If a female of childbearing potential, willing to use 2 methods of birth control or willing to abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug.
10. Experienced resolution of toxic effect(s) of the most recent prior anti-cancer therapy to Grade ≤1 (except alopecia or neuropathy). If patient underwent major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
11. Able to understand and give written informed consent and comply with study procedures.

EXCLUSION CRITERIA:

Patients meeting any of the following criteria are not eligible for study participation:

1. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Medical Monitor.
2. Active autoimmune disease including active diverticulitis, symptomatic peptic ulcer disease, colitis, or inflammatory bowel disease that has required systemic treatment in past 2 years (i.e., with disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
3. Previously treated with a PD-1/PD-L1-blocking antibody (e.g., atezolizumab, nivolumab, pembrolizumab) or a histone deacetylase inhibitor (e.g.., vorinostat, belinostat, romidepsin, panobinostat)

4. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator, including, but not limited to:
   - History of immune deficiencies or autoimmune disease (refer to Appendix 3 for complete list)
   - Myocardial infarction or arterial thromboembolic events within 6 months prior to screening or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QTc interval > 470 msec.
   - Uncontrolled hypertension or diabetes mellitus.
   - Another known malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia [CIN]/cervical carcinoma *in situ* or melanoma *in situ*). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years.
   - Active infection requiring systemic therapy.
   - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. (see inclusion criterion 5)
5. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.
6. Received a live vaccine within 30 days of the first dose of treatment. (Inactivated forms of influenza vaccinations can be given during influenza season only (approximately October to March in the Northern hemisphere and April to September in the Southern Hemisphere)).
7. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to enrollment or who has not recovered (i.e., ≤Grade 1 at enrollment) from AEs due to mAb agents administered more than 4 weeks earlier.
8. Prior chemotherapy within 3 weeks, targeted small molecule therapy or radiation therapy within 2 weeks prior to enrollment, or who has not recovered (i.e., ≤Grade 1 at enrollment) from AEs due to a previously administered agent.

   Note: Patients with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.
9. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to the first dose of treatment.
10. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.
11. Currently receiving treatment with any other agent listed on the prohibited medication list (protocol section 9.12
12. If female, is pregnant, breastfeeding, or expecting to conceive starting with the screening visit through 120 days after the last dose of study drug.
13. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
14. Known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative]). Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization. Patients

positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

15. Allergy to benzamide or inactive components of entinostat.
16. History of allergies to any active or inactive ingredients of atezolizumab.
17. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

Investigational Product:

Entinostat

Entinostat is a synthetic small molecule bearing the chemical name 3-pyridylmethyl-N-{4-[(2-aminophenyl)carbonyl] benzyl}carbamate and the molecular formula $C_{21}H_{20}N_4O_3$, with a molecular weight of 376.41. Entinostat is classified as an antineoplastic agent, specifically functioning as an inhibitor of histone deacetylases by promoting hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes that leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis. Entinostat is given orally and is supplied in two strengths of film-coated tablets containing 1.0 mg (pink to light red) or 5.0 mg (yellow).

Entinostat should be stored at a controlled room temperature of 15°C–25°C (59°F–77°F).

Atezolizumab

Atezolizumab is a humanized monoclonal antibody designed to target PD-L1 expressed on tumor cells and tumor-infiltrating immune cells, and prevent binding to PD-1 and B7.1 on the surface of T cells. This may enable the activation of effector T cells as well as recruitment of other T cells to attack the tumor, thus empowering the body's own immune system to fight multiple types of cancer.

Atezolizumab drug product is provided in a single-use, 20-mL USP/PH. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. The atezolizumab drug product is formulated as 60 mg/mL of atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Statistical Considerations:

The safety and efficacy analyses will be presented by study phase. For the Dose Determination Phase, tabulations will be provided by dose cohort and overall. Some analyses may be performed based on the Dose Determination and Expansion Phases combined.

Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

An interim safety analysis is planned following the completion of Cycle 1 for the first 20 patients enrolled in the Phase 2 expansion phase and will utilize a Data Safety Monitoring Board.

Treatment-emergent AEs reported during the study will be tabulated and listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Tables will display number and percentage of patients experiencing the event for the following categories: all AEs; AEs considered related to study treatment; AEs by severity; DLTs; AEs occasioning treatment delay, reduction or discontinuation; and serious adverse events (SAEs). For the Dose Determination Phase, the observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experienced DLT with a 2-sided 95% exact binomial confidence interval (CI).

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: enrollment value, minimum and maximum post enrollment values, average post enrollment value, and last post enrollment value. Standard shift tables will also be prepared presenting worst post enrollment toxicity grade versus enrollment. Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values.

Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set. An interim efficacy analysis is planned after 45 PFS events have occurred in the Phase 2 study portion.

PFS is the primary endpoint for the Expansion Phase of this study. PFS is defined in the conventional manner as the number of months from the randomization date to the earlier of documented progressive disease or death due to any cause. Progressive disease will be assessed by the local investigator using RECIST 1.1. The disease progression date and censoring date will be based on published conventions (FDA 2007). Sensitivity analyses will be performed to identify asymmetry between treatment arms for the frequency of missed disease assessments, deviations of the actual disease assessment times from the planned assessment times. Alternative censoring conventions will also be used to assess among other concerns, dropouts with undocumented progressive disease. PFS will be summarized descriptively using the Kaplan-Meier method. The primary inferential comparison between treatment arms will be performed using the log-rank test stratified by the randomization stratification factor of geographic location. Estimation of the hazard ratio for treatment arm will be determined using a stratified Cox proportional hazards model, without any other covariate. The corresponding results from the log-rank test and Cox model without stratification will be reported as supplemental analyses.

The statistical methods to be used for the analysis and reporting of the secondary efficacy endpoints are described in Section 13.5 of the protocol.

Procedures: The Schedule of Study Assessments is included in Table 1-1 below.

Table 1-1 Schedule of Study Assessments

Procedure	Screening (D -21 to -1)	Combination Therapy						EOT (≤7 days of last study drug dose)	Safety F/U (≤30 days of EOT)	Post-Study F/U [1]
		C1			C2		≥C3			
		D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
Provision of written informed consent	X									
Demographics	X									
Medical and disease history	X	X								
Complete physical examination	X[2]	X[2]						X	X	
Symptom-directed physical examination		X	X	X	X	X	X			
ECG	X						X[3]	X		
Vital signs, weight (height at screening only)	X	X			X		X	X	X	
ECOG performance status[4]	X	X			X		X	X	X	
Radiological Imaging, Disease assessment	X[5]						X[6]	X[7]		X[7]
Pregnancy testing	X	X[8]								
Hematology, coagulation studies[9], and clinical chemistries[10, 11]	X	X[11]	X	X	X	X	X	X		
Blood sample for immune correlates[12]		X[12]			X[12]	X[12]	X[12]	X[12]		
Blood sample for TRegs/KI67		X[13]			X[13]		X[13]	X[13]		
Blood sample for atezolizumab serum biomarker		X[13]			X[13]	X[13]	X[13]	X[13]		
Blood sample for atezolizumab plasma biomarker		X[13]			X[13]	X[13]	X[13]	X[13]		
Blood sample for protein lysine acetylation[13]		X[14]		X[14]						
Tissue sample biopsy for immune correlates (also archival tissue when available)	X[15]					X[15]		X[15]		
Entinostat self-administration		Self-administered weekly starting on C1D1; C1D1 ≤3 business days of								

Procedure	Screening (D -21 to -1)	Combination Therapy						EOT (≤7 days of last study drug dose)	Safety F/U (≤30 days of EOT)	Post-Study F/U [1]
		C1			C2		≥C3			
		D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
		enrollment								
Atezolizumab administration[16]		X			X		X			
Blood sample for entinostat pharmacokinetics[17]		X[17]	X[17]	X[17]	X[17]					
Blood sample for atezolizumab pharmacokinetics and anti-therapeutic antibodies[18]		X[18]			X[18]			X[18]		X[18]
Pre-treatment/concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	
Study drug compliance assessment		X	X	X	X	X	X	X		

[1] *After the Safety F/U visit, patients who have not experienced PD are followed (including radiological assessments) q6 weeks (+/- 3 d) through study week 36 and then every 9 weeks (+/- 3 d) thereafter until unequivocal PD. Thereafter, they are contacted q3 months until death or study closure for information on PD, alternate treatments and survival status.*

[2] *If the screening complete PE was performed within 7 days before C1D1, then a symptom-directed examination may be performed at enrollment.*

[3] *An ECG is to be performed pre-dose on C3D1 (- 3d) and then every 3 cycles (- 3d) thereafter. An ECG may be repeated anytime, as clinically indicated.*

[4] *Also performed if fluid retention occurs*

[5] *Performed only if last scan was performed >28 days before C1D1*

[6] *Patients will have radiological disease assessments performed every 6 weeks (+/-3 d) through week 36 (Week 6, 12, 18, etc.) and then q9 weeks (+/- 3 d) hereafter during treatment and for patients who have not yet progressed when discontinuing study treatment, until progression based on this schedule.*

- *Partial or complete response should be confirmed by a repeat tumor imaging assessment at the earliest 4 weeks after the first indication of response, or at the next scheduled scan if on a 6 week schedule, whichever is clinically indicated.*
- *If radiologic imaging demonstrates initial evidence for PD, tumor assessment should be repeated at the earliest of 4 weeks, or preferably on the study schedule of 6 weeks, in order to confirm PD.*

[7] *Performed only if radiological progression was not previously observed on study.*

[8] *For female patients of child-bearing potential, a required serum pregnancy test is to be performed during screening and a urine test within 3 days before the first study drug dose. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.*

[9] *Analytes tested: RBC, WBC with absolute counts of individual cell types, platelet count, HGB and HCT. Screening only also includes: prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT).* [10] *Analytes tested: ALT, AST, albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, sodium, potassium, chloride, bicarbonate, glucose, LDH, phosphorus, total protein and uric acid. Magnesium and TSH at enrollment only, unless clinically indicated.*

[11] Performed only if screening laboratory tests performed >7 days prior to enrollment; screening laboratory results remain as the baseline entry criteria and abnormalities thereafter are to be noted as, and treated as, adverse events
[12] Samples collected pre-dose; not collected after C3 D1 except at EOT.
[13] Samples collected pre-dose.
[14] Sample taken before any study drug administration.
[15] Fresh tumor core biopsy during screening from all patients on a mandatory basis; required on C2D15 (+/-3 days) funtil 20 samples are obtained in the Phase 2, but optional for everyone else; optional for all patients at disease progression and end of study treatment. Archival tissue is collected at screening when available.
[16] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes and if well tolerated, all subsequent infusions as well. Vital signs should be determined up to 60 minutes before each infusion as well as during and after infusion if clinically indicated.
[17] C1D1 samples are taken pre-dose and 2-4 h post entinostat dosing; C1D8 and C1D15 taken any time after entinostat dosing; C2D1 taken pre-dose
[18] C1D1 samples for PK and ADA are taken pre-dose and again 30 minutes (+/- 10 minutes) post infusion (PK only); C2D1, C4D1 are taken pre-dose; EOT and, if patient is still being following per protocol on day 120 after coming off study treatment, a PK sample should be collected

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2.STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADaM	Analysis Dataset Model
AE	Adverse event
AESI	Adverse Event of Special Interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ATA	Anti-tumor activity
aTNBC	Advanced Triple Negative Breast Cancer
AZA	5-Azacitadine
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CBR	Clinical benefit rate
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CSC	Cancer stem cell
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation/Acronym	Definition
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
D	Day
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
F/U	Follow-up
FAS	Full Analysis Set
FDG	18F-deoxyglucose
FoxP3	Forkhead box P3
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage-colony stimulating factor
G-MDSCs	Granulocytic myeloid-derived suppressor cells
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

Abbreviation/Acronym	Definition
ICH	International Council for Harmonisation
ID	Identification
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
ILD	Interstitial lung disease
IND	Investigational New Drug Application
INR	International normalized ratio
irAE	Immune-related adverse events
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous(ly)
LDH	Lactic dehydrogenase
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Inevaluable
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival

Abbreviation/Acronym	Definition
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	By mouth
PP	Per-protocol
PR	Partial response
PT	Prothrombin time
Q2W	Every other week (i.e., every 2 weeks)
Q3W	Every 3 weeks
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommend Phase 2 Dose
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Stable Disease
SDTM	Study Data Tabulation Model
SIA	Systemic immune activation
SOC	System organ class
SOD	Sum of Diameters
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine

Abbreviation/Acronym	Definition
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TMTB	Total Measured Tumor Burden
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
V-type	Variable-type
WBC	White blood cell (count)
WoCBP	Women of Child Bearing Potential

3.OBJECTIVES

3.1 Primary

The primary study objectives are:

Phase 1b (Dose Determination Cohort): To determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of entinostat (SNDX-275) given in combination with atezolizumab.

Phase 2 (Expansion Cohort): To perform an evaluation of the efficacy of entinostat at the RP2D in combination with atezolizumab in patients with aTNBC, as determined by the duration of progression-free survival (PFS) based on the local investigator's assessment of progressive disease using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) .

3.2 Secondary

Secondary study objectives are:

Efficacy: In Phase 2, to evaluate the efficacy of entinostat in combination with atezolizumab in patients with aTNBC, as determined by:

- PFS based on immune-related RECIST (irRECIST)
- Overall response rate (ORR) (i.e., complete response [CR] or partial response [PR]) based on RECIST 1.1 and irRECIST
- Clinical benefit rate (CBR) (i.e. CR or PR or stable disease [SD] for at least 24 weeks) based on RECIST 1.1 and irRECIST
- Overall survival (OS)

In patients with best overall response of CR or PR:

- Duration of response (DOR)
- Time to response (TTR)

Safety: To evaluate safety and tolerability of entinostat in combination with atezolizumab, as measured by clinical adverse events (AEs) and laboratory parameters.

3.3 Exploratory

The exploratory study objectives are to:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4. ENDPOINTS

4.1 Efficacy

The primary efficacy endpoint is:

- PFS, as determined by the local investigator using RECIST 1.1

Secondary endpoints:

- PFS determined by the local investigator using irRECIST
- ORR (CR or PR) by RECIST 1.1 and irRECIST
- CBR (CR, PR, or SD for at least 24 weeks) by RECIST 1.1 and irRECIST
- OS

In patients who experience a response to treatment (i.e., CR or PR):

- DOR
- TTR

4.2 Safety

Safety endpoints are:

- Determination of DLT, MTD and RP2D
- AEs
- Clinical laboratory parameters, Vital Signs, Physical Exam

4.3 Exploratory

Exploratory endpoints include:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5. BACKGROUND AND RATIONALE

Triple negative breast cancer (TNBC) represents 15-20% of newly diagnosed breast cancer cases, and is associated with a younger age and advanced stage at diagnosis, increased risk of visceral metastasis and poorer outcome. The five-year survival rate for women diagnosed with Stage IV TNBC is only 22% with limited treatment options. Development of novel approaches to improve the treatment outcome for TNBC patients remains a significant unmet challenge.

Immuno-oncology is an emerging field of cancer medicine that has focused on the development of therapeutic approaches designed to activate the immune system to find and destroy cancer cells. The immune system consists of two parts, the innate immune system and the adaptive immune system and both play a role in an immune mediated effective anti-tumor immune response. The innate immune system, composed of key cells such as natural killer (NK) and neutrophils, is non-specific and is designed to rapidly identify and eliminate immediate threats to the body, such as infections and other pathogens. The adaptive immune system, composed of B cells, T cells and other immune regulatory cells, targets specific antigens and provides a long-term response, known as immunologic memory, to antigens it recognizes as foreign.

Many tumors have the ability to evade both the innate and adaptive immune system through direct cellular interactions and recruitment of immune-suppressive cells to the area surrounding the tumor (Wu 2015). Cancer cells can express proteins on their cell surface known as check point proteins, such as PD-L1 and programmed cell death protein ligand 2, or PD-L2, that block the ability of immune cells known as cytotoxic T cells to kill cancer cells (Mahoney 2015; Sharma 2015). Antibodies that block PD-L1 or PD-L2 restore the ability of cytotoxic T cells to kill cancer cells and have shown great clinical promise. Positive results notwithstanding, durable responses have been observed in only a relatively small population of patients, with overall response rates below 30% depending on tumor type; this suggests that additional strategies enhancing the anti-tumor immune response are needed to improve the survival of cancer patients (Mahoney 2015; Sharma 2015).

Research to identify the basis for the limited efficacy of recently developed immune therapies has provided investigators with an appreciation for the role that specific immune regulatory cells, such as MDSCs and Tregs, have in dampening the cytotoxic T cell response (Joyce 2015; Mahoney 2015; Sharma 2015). MDSCs and Tregs localize in the area surrounding the tumor and, together with the immune checkpoints, play a significant role in helping a tumor evade detection and elimination by the immune system (Marvel 2015; Adeegbe).

MDSCs are immature myeloid cells that are activated by disease or injury and are generally increased in cancer patients. The primary function of MDSCs is to suppress an activated T cell immune response through the production and secretion of enzymes that deplete key amino acids required for the growth and function of cytotoxic T cells (Marvel 2015). High concentrations of circulating MDSCs in various cancers, including breast, lung, head and neck, correspond with a poor prognosis and limited response to cancer therapy (Liu 2010; Najjar 2013; Solito 2011; Weed 2014). Recent data further indicate that high concentrations of circulating MDSCs in melanoma patients are inversely correlated with clinical response to immune checkpoint inhibitors suggesting that targeting MDSCs may offer new therapeutic opportunities for enhancing the anti-tumor response to immune checkpoint inhibitors (Weber 2015).

Tregs are a second type of immune suppressor cell and are recruited to sites of active immune response in order to shut down the cytotoxic T cell response (Adeegbe 2013; Zhang 2015). Unlike MDSCs, which are found in activated states in circulating blood, Tregs are recruited to the tumor microenvironment and activated by local signals from the cancer cell (Adeegbe 2013; Zhang 2015). As with MDSCs, an increase in the concentration of activated Tregs correlates with poor prognosis in a number of tumor types including breast, colorectal, and ovarian cancers (Freiser 2013; Zhang 2015). Tregs suppress cytotoxic T cell responses through the secretion of cytokines that inhibit the growth of cytotoxic T cells. In addition Tregs can cause other immune regulatory cells in the tumor microenvironment to secrete immune suppressive enzymes (Freiser 2013; Zhang 2015). Inhibiting Tregs may therefore relieve immune suppression in a way similar and potentially complementary to that of other immune-targeted approaches.

Separate preclinical studies have demonstrated that entinostat is a dual inhibitor of immune suppressor cells and targets both MDSCs and Tregs. Figure 5-1 below shows that entinostat reduces the growth of MDSCs at concentrations that spare the growth of cytotoxic T cells. Approximately half of the MDSCs are stopped from growing at 200 nM of entinostat, which is 35 times less than the concentration of entinostat that stops half of the cytotoxic T cells from growing (Kim 2014).

Investigators have previously demonstrated FOXP3, a protein involved in Treg function, is an indicator of Treg immune suppressor activity. Figure 5-2 below shows that entinostat reduces the expression of FOXP3 protein in Tregs, when administered in an animal cancer model, thus demonstrating entinostat's ability to inhibit Treg immune suppressor activity (Shen 2012).

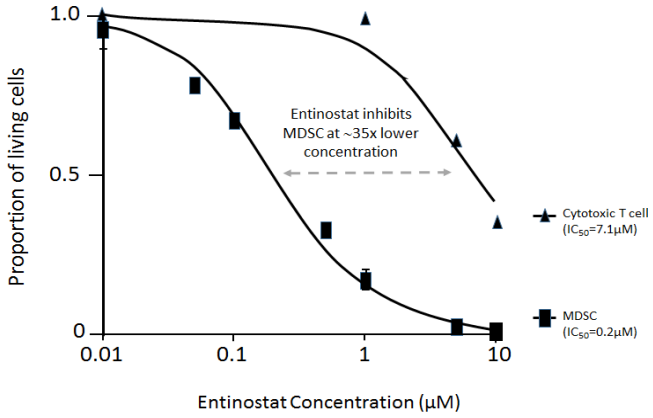


Figure 5-1 (Kim 2014)

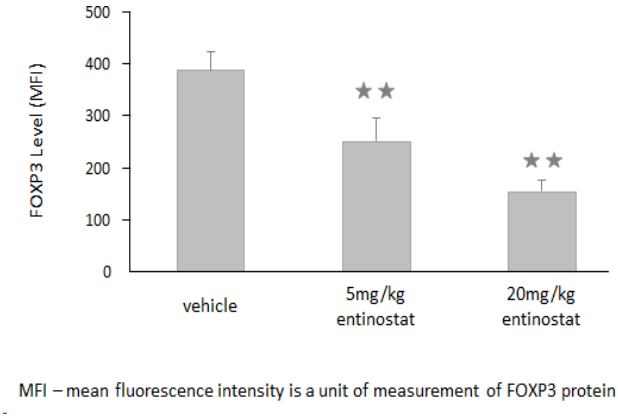
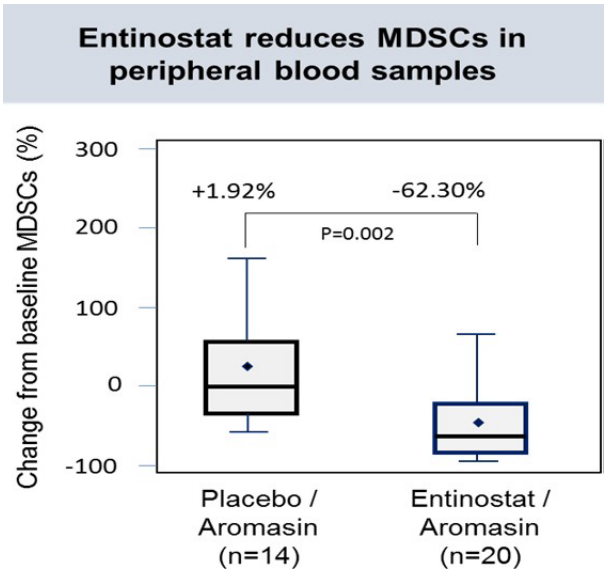


Figure 5-2 (Shen 2012)

In order to determine whether the effects observed in preclinical research studies can also be observed in cancer patients treated with entinostat, an analysis was conducted on immune cells in blood samples collected from a subset of patients treated in ENCORE 301, a Phase 2b clinical trial in advanced HR+ breast cancer patients. As shown in Figure 5-3 below, in these peripheral blood samples, a statistically significant reduction in the concentration of circulating MDSCs was observed in patients treated with the combination of entinostat and exemestane, a hormone therapy, but not in patients treated with the combination of placebo and exemestane.

Figure 5-3

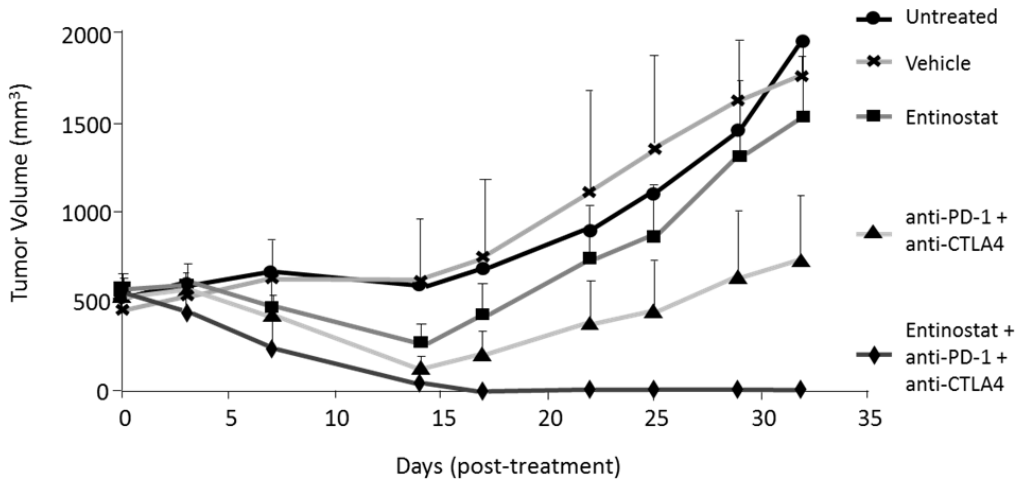


Data on file

Data Supporting Entinostat in Combination with Immune Checkpoint Inhibitors.

Preclinical. In order to determine whether entinostat could be combined effectively with immune checkpoint inhibitors, entinostat was tested in combination with anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4, or CTLA4, directed antibodies in immune-resistant animal models. As shown in Figure 5-4 below, the elimination of both primary and metastatic tumors was observed in a 4T1 mouse triple negative metastatic breast cancer model that was treated with entinostat together with dual PD-1/CTLA4 checkpoint inhibition. In this experiment, it was observed that entinostat reduced the number and activity of MDSCs, rather than attacking and destroying replicating cells like standard chemotherapy drugs. The significant anti-tumor effect of entinostat combine with immune checkpoint blockade in the 4T1 TNBC mouse model supports the clinical testing of entinostat combined with atezolizumab in TNBC.

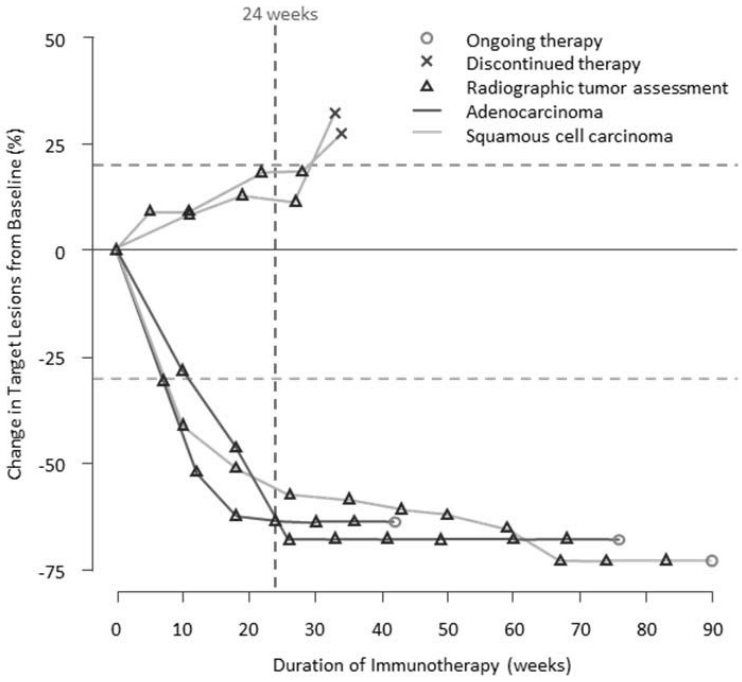
Figure 5-4



Source: (Kim 2014)

Clinical. In patients who were treated in two unrelated clinical trials, physicians at JHU observed preliminary evidence for the potential beneficial effects of combining entinostat with a PD-1 or PDL-1 inhibitor. In a heavily pre-treated metastatic NSCLC population, patients given the combination of entinostat and azacitidine, an approved agent, achieved few objective responses and only a modest 3% overall response rate (Juergens 2011). However, investigators observed that patients who received the combination of entinostat and azacitidine and subsequently received immune checkpoint therapy demonstrated a higher response rate than expected for this patient population. Figure 5-5 below illustrates that all five patients who received either nivolumab, an approved anti-PD-1, or an investigational PDL-1 inhibitor as their next therapy derived durable clinical benefit. Three of the patients had durable responses and two had durable stable disease. This enhanced response rate was better than the 15% response to nivolumab alone observed in a similar advanced NSCLC population and led investigators to hypothesize that the prior effect of the combination of entinostat and azacitidine therapy was "priming" the tumors to the subsequent immune therapy (Wrangle 2013). To confirm these findings and further explore the ability of the combination of azacitidine and entinostat to enhance the response of NSCLC patients to nivolumab, the investigators at JHU have initiated a follow-on randomized Phase 2 clinical trial, J1353.

Figure 5-4



Data on file

Based on these findings it is hypothesized that entinostat combined with a PD-1/PD-L1-blocking antibody, atezolizumab, will result in an improvement in PFS for the combination compared to atezolizumab alone.

5.1 Study Treatment

5.1.1 Entinostat (SNDX-275)

Deoxyribonucleic acid (DNA) within the cell nucleus combines with a class of proteins called histones to form chromatin. Histones have amino terminal groups that are positively charged and are deacetylated by HDACs. The positive charge tightly binds the histones to the negatively charged DNA phosphodiester backbone. Gene transcription and expression are inhibited by such a condensed conformation of the DNA. Histone acetyltransferases acetylate the amino terminal ends and neutralize their positive charges, thus leading to a more open chromatin conformation, facilitating DNA transcription.

Entinostat (SNDX-275), an orally available synthetic pyridylcarbamate licensed from Bayer Schering AG by Syndax Pharmaceuticals and previously named MS-275, inhibits histone

deacetylases (HDACs). Entinostat promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes. This ultimately leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis (Hess-Stumpp, 2007).

Altered activity of HDACs and inactivation of histone acetyltransferases within transformed cells are key events that affect chromatin remodeling. There is evidence that HDACs are associated with a wide range of tumors including melanomas, neuroblastomas, lymphomas, and lung, breast, prostate, ovarian, bladder, and colon cancers. In a number of *in vitro* models, HDAC inhibitors triggered growth arrest and induced cell differentiation or apoptosis. In acute promyelocytic leukemia, recruitment of HDACs by aberrant fusion proteins repressed constitutive gene transcription and thus prevented promyelocytic differentiation.

Entinostat also induced histone hyperacetylation and induced expression of various tumor suppressor genes. Various *in vitro* studies in a range of human cancer cell lines have demonstrated the antiproliferative activity of entinostat. *In vivo*, entinostat inhibited the growth of a range of human tumor xenograft model, including lung, prostate, breast, pancreatic, renal cell, and glioblastoma.

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

5.1.1.1 Entinostat in Patients with Solid Tumors, including breast cancer

To date, entinostat has been investigated alone or in combination in >1000 patients with cancer in clinical studies. In breast cancer, entinostat has been studied in a randomized phase 2 clinical trial sponsored by Syndax, ENCORE 301, in patients with ER+ metastatic breast cancer. ENCORE-301 was a placebo-controlled, double-blind trial of exemestane in combination with entinostat (EE) versus exemestane plus placebo (EP). The primary endpoint of PFS was met, with EE resulting in a median of 4.3 months and EP a median of 2.3 months. Overall survival, an exploratory endpoint, showed a survival benefit of approximately 8 months in favor of EE (28.1 months) versus EP (19.8 months), In 2014 the FDA granted Breakthrough Therapy designation for entinostat combined with exemestane in metastatic hormone receptor-positive breast cancer in post-menopausal women whose disease has progressed following non-steroidal aromatase inhibitor (AI) therapy based on these results. A phase 3 registration study,

E2112, has been designed to confirm the ENCORE 301 results and is currently being conducted by ECOG-ACRIN under sponsorship from the NCI under a Special Protocol Assessment.

In clinical trials to date, entinostat has been well tolerated at the doses and schedules investigated. The AEs reported most frequently included gastrointestinal (GI) disturbances, primarily nausea with or without vomiting and diarrhea; fatigue; and hematologic abnormalities, primarily anemia, thrombocytopenia, neutropenia, and leukopenia. Most of these events were Grade 1 or 2 in severity and non-serious. Grade 3 and 4 hematologic abnormalities are more commonly seen in patients with hematologic malignancies and are less common in patients with solid tumors.

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

5.1.2 Atezolizumab

5.1.2.1 Background

Atezolizumab (MPDL3280A) is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 in the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function and depletion of cells expressing PD-L1. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor, PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy for solid tumors and hematologic malignancies in humans.

Refer to the current atezolizumab IB for detailed background information on this drug product.

5.1.2.2 Pharmaceutical and Therapeutic Background

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune

responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed death ligand-2 [PD-L2]). The structures of murine PD-1 alone (Zhang 2004) and in complex with its ligands have been resolved (Lazar-Molnar 2008; Lin 2008), and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (Cheng 2013). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade (Sheppard 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (Ott 2013). PD-1 was shown to be expressed on activated lymphocytes, including peripheral $CD4^+$ and $CD8^+$ T cells, B cells, T regs and natural killer cells (Yao 2014). Expression has also been shown during thymic development on $CD4^-CD8^-$ (i.e., double-negative) T cells (Nishimura 1996), as well as subsets of macrophages (Huang 2009) and dendritic cells (Pena-Cruz 2010). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (Keir 2008). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (Keir 2008). Both ligands are type I transmembrane receptors containing both Ig variable- and Ig constant-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (Karim 2009; Taube 2012), which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors

(Sanmamed 2014). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian 2012).

5.1.2.3 Atezolizumab Non-Clinical Studies Summary

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients.

Refer to the Atezolizumab Investigator's Brochure (IB) for details on the nonclinical studies.

5.1.2.4 Atezolizumab Clinical Studies Summary

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions). The single-agent safety and efficacy data available to date are from the following studies: one Phase Ia (Study PCD4989g) and two Phase II studies (Studies GO28625 [FIR] and GO28753 [POPLAR]).

Clinical benefit from atezolizumab monotherapy was observed in a broad range of malignancies including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, urothelial bladder cancer (UBC), head and neck cancer, gastric cancer, breast cancer and sarcoma. Results suggest that PD-L1 expression in the tumor microenvironment is associated with an increased probability of clinical benefit with atezolizumab.

Across all these patients, fatigue was the most frequently reported adverse event. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been monitored closely during the clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal and respiratory events.

In trials investigating atezolizumab both as a single agent and in combination with chemotherapy, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Currently, no maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of adverse events have been determined.

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

5.2 Study Rationale

Treatment of TNBC represents a significant challenge due to the lack of clinically validated targets that are available for the other breast cancer subtypes. Preliminary data has indicated that treatment with immune checkpoint inhibitors targeting PD-1 such as pembrolizumab and PD-L1 such as atezolizumab results in approximately an 18-19% response rate in women with TNBC who also test positive for PD-L1 expression. While these data are promising, the benefit appears to be restricted to a relatively small fraction of the total TNBC patient population. Combination strategies to increase the clinical benefit of PD-1 / PD-L1 inhibitors in TNBC are the focus of intense research efforts. Preclinical testing in the 4T1 mouse model of TNBC indicate that entinostat combined with immune checkpoint blockade results in complete inhibition of primary tumors and metastases. The mechanism for this combined anti-tumor effect was determined to be entinostat's ability to inhibit the growth and function of MDSCs, an immune suppressor cell shown to block the anti-tumor T cell immune response. These data provide the basis for clinical testing of entinostat combined with atezolizumab in TNBC patients.

5.3 Rationale for the Dose Selection

5.3.1 Entinostat

Entinostat has been evaluated *in vitro*, in nonclinical *in vivo* studies, and in Phase 1 and 2 studies in patients with various solid tumors and hematological malignancies at doses between 2 and 12 mg/m^2 and at dosing frequencies ranging from once daily to every 2 weeks. Increased histone acetylation was observed at the lowest dose evaluated with the effect persisting at least 48 hours post-dose. Pharmacokinetic (PK) studies of entinostat have

indicated a long half-life of entinostat, ranging from 40 hours to 120 hours. Consistent with this long half-life, entinostat concentrations were detectable 168 hours post-dose at doses of 2 to 12 mg/m^2.

The MTD for single agent entinostat in non-hematologic indications was established as 4 mg/m^2 weekly x 3 followed by a 1 week rest, or 10 mg/m^2 every other week continuously.

PK analyses have demonstrated ~40% variability in the clearance of entinostat. However, when clearance was adjusted for body surface area (BSA), the inter-patient variability was similar. In a linear regression analysis on factors that may contribute to this variability, ideal body weight, lean body mass, body weight, and body mass index, were not significant covariates. As a result of this analysis, fixed dosing is considered to be as accurate as dosing based on BSA (Alao, 2004).

Entinostat given once weekly continuously at a dose of 5 mg (in combination with the aromatase inhibitor exemestane) in patients with locally advanced or metastatic breast cancer or given every other week continuously at a dose of 10 mg (in combination with erlotinib) in patients with stage IIIB/IV NSCLC, was well tolerated. The AE profile at these dose schedules was consistent with previous clinical experience, with the most common AEs being fatigue and gastrointestinal disturbances, (nausea, vomiting, and diarrhea).

Based on the clinical experience with entinostat, fixed dose of 5 mg given weekly has been selected as the starting dose for this study, with dose initial de-escalation to 3 mg and secondly to 2 mg, if toxicity occurs with the combination treatment.

5.3.2 Atezolizumab

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below.

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity (ATA) has been observed across doses from 1 mg/kg to 20 mg/kg administered q3w. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg q3w, overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies. Detectable ATAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts whether administration of higher doses to patients with both detectable ATAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ATAs and safety or efficacy has been observed. Available data suggest that the development of detectable ATAs does not appear to have a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg administered q3w in most patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg q3w dose levels have maintained target trough concentrations of drug despite the detection of ATAs.

Currently available PK and anti-treatment antibody data suggest that the 15-mg/kg atezolizumab q3w regimen *(or fixed-dose equivalent)* would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and potential effect of ATAs that could lead to sub-therapeutic levels of atezolizumab relative to the 10-mg/kg q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, a 20 mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg q3w is selected (equivalent to a body weight–based dose of 15 mg/kg q3w).

Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation and allows for a convenient integration with common therapeutic regimens.

5.4 Hypothesis

Phase 1b: The combination of atezolizumab and entinostat at a biologically active dose will be sufficiently safe and well tolerated to warrant further investigation.

Phase 2: Entinostat at the dose determined in Phase 1b combined with atezolizumab will result in an improved Progression-Free Survival compared to atezolizumab alone.

6. EXPERIMENTAL PLAN

6.1 Study Design

Study SNDX-275-0602 (TRIO025) is a randomized, placebo-controlled, double-blind, multicenter phase 2 study evaluating the combination of atezolizumab with or without entinostat in patients with aTNBC with a Phase 1b lead-in phase to determine the recommend phase 2 dose of entinostat.

Figure 6-1 Flowchart of Dose Determination Advancement

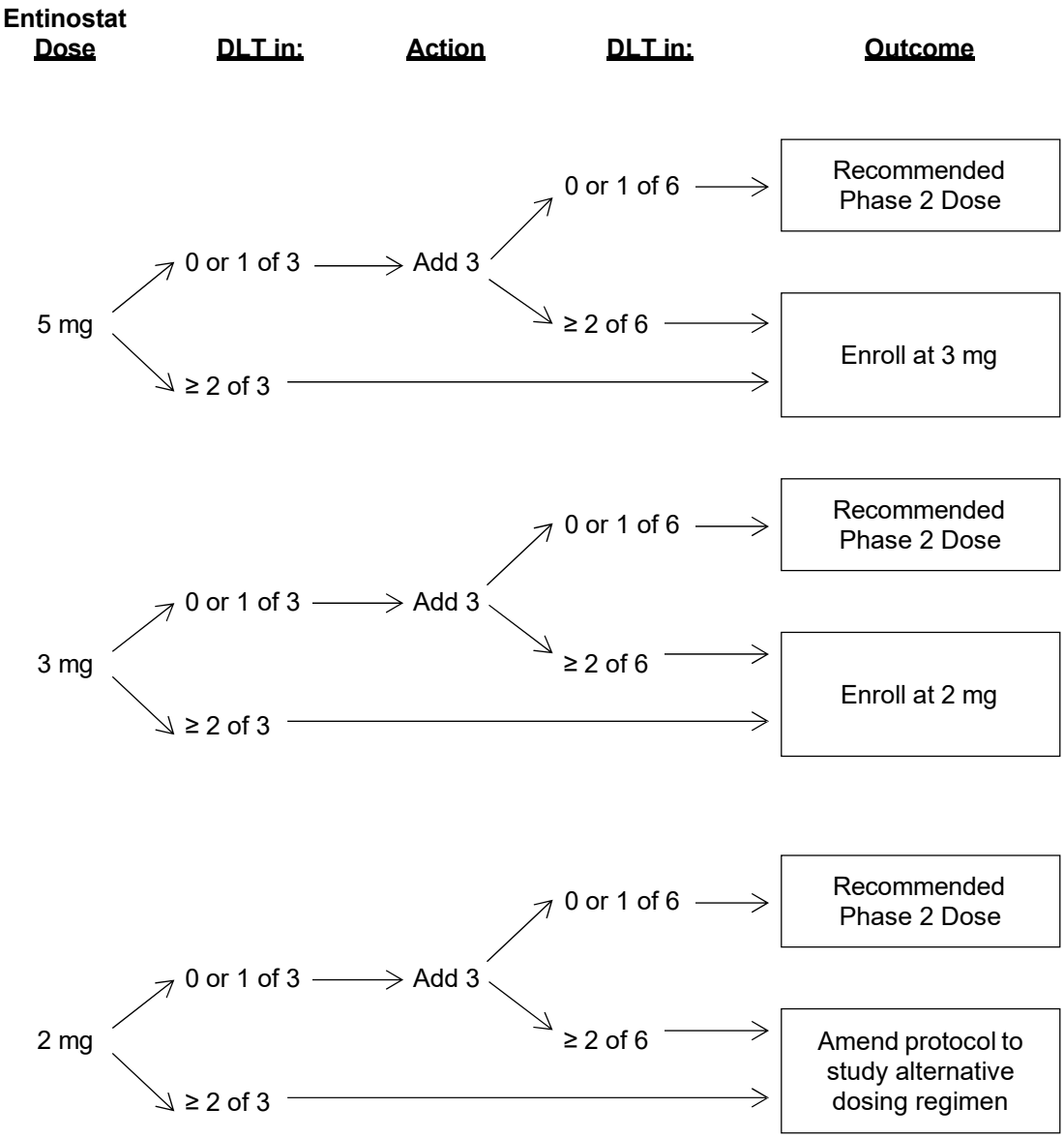
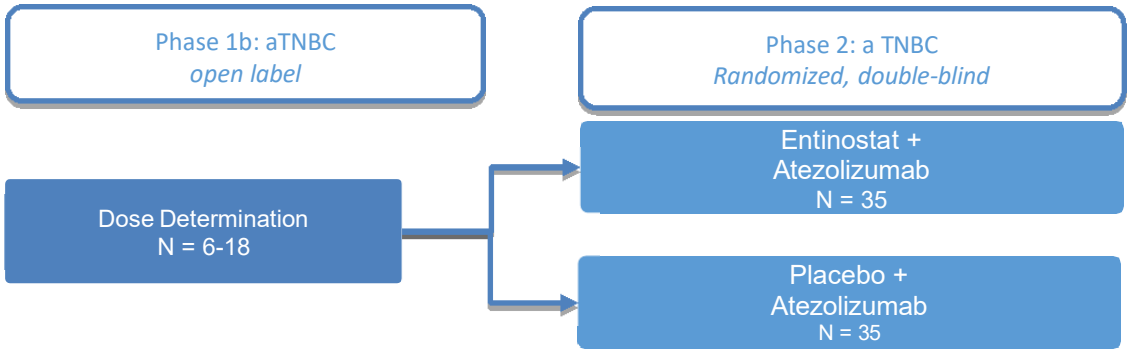


Figure 6-2 Study Schema



Phase 1b sites will be notified by TRIO regarding the availability of slots in a given cohort, observation of DLTs and entinostat dose levels, to assist with screening activity.

Regardless of phase, patients will be screened for study eligibility within 21 days before enrollment. Patients who are determined to be eligible, based on screening assessments, will be enrolled in the study within 3 business days of starting study treatment on Cycle 1, Day 1 (C1D1).

A cycle is 21 days in length. During treatment, patients will attend study center visits and study evaluations will be performed on C1D1, C1D8, and C1D15; D1 and D15 of C2; and on D1 of each cycle thereafter.

Fresh tumor tissue core biopsy (image-guided if applicable) will be collected during the study as follows.:

- During **screening** from **all** patients on a **mandatory** basis. Archival tumor tissue will also be collected when available.
- On **C2D15 (+/-3 days)** on an **optional** basis from patients in **the Phase 1b Dose Determination Phase**. All patients in the Dose Determination Phase will be strongly encouraged to undergo an optional biopsy in order to help understand dose-immune correlate effects.
- On **C2D15 (+/-3 days)** on a **mandatory** basis until **20 samples are obtained in the Phase 2 Expansion Phase** and on an **optional** basis for subsequent patients in this phase.
- At the end of study treatment prior to the start of another systemic therapy, on an **optional** basis for all patients.
- At disease progression on an **optional** basis for all patients.

If, based on an interim review of tumor tissue data from the initial patients in the Expansion Phase, such data are considered informative, tumor tissue samples will be collected on a mandatory basis from all subsequent patients on C2D15 (+/-3 days). Alternatively, if such data are not considered informative, subsequent samples will not be collected.

Blood for immune correlates is to be collected pre-dose on each of C1D1, C2D1, C2D15, C3D1 and at the end of treatment. Blood for protein lysine acetylation is to be collected pre-dose on C1D1 and C1D15. Patients will have radiological disease assessments performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) beginning at C1D1, during study treatment through week 36 or until progressive disease. If progressive disease has not occurred by week 36, radiological assessments will then be done every 9 weeks (+/-3 days) until progressive disease. If a patient comes off study for reasons other than progressive disease, radiological assessments will continue at 6 week intervals until what would have been study week 36 and then switch to a 9 week interval, until progressive disease is radiologically documented. Disease will be assessed by computed tomography (CT), magnetic resonance imaging (MRI), and bone scans, as appropriate, and response will be assessed by the Investigator using irRECIST. The same imaging modality should be employed for all follow-up scans as was used at baseline.

Safety will be assessed during the study by documentation of AEs, clinical laboratory tests, physical examination, vital sign measurements, ECGs, and Eastern Cooperative Oncology Group (ECOG) performance status.

Within 7 days of the last dose of study treatment, all patients will complete an End of Treatment (EOT) visit, and a Safety Follow-up (F/U) visit will be required 30 days (+/- 3 days) thereafter. After completion of the 30-day F/U visit, patients who have experienced progressive disease are to be contacted every 3 months thereafter for survival status and information regarding treatment regimens, until death or closure of the study by the Sponsor. Those patients who have not experienced progressive disease, will continue radiological disease assessments as noted above.

Phase 1b (Dose Determination): This study phase employs a classical 3+3 design, with the determination of DLT and the MTD or RP2D based on the combination of entinostat with atezolizumab in C1. Six patients will need to be treated in a dose level for it to be considered MTD or the RP2D.The recommended dose for Phase 2 investigation will be the higher of either 2, 3 or 5 mg weekly PO that results in less than a 33% incidence of DLT. The final determination of the optimal dose for further use will consider both acute and cumulative toxicities; the incidence of required dose delays, reductions, and discontinuations; and the overall facility of administration in clinical practice.

The initial 3-6 patients will receive entinostat at a starting dose of 5 mg (Dose Group 1) on D1, D8, and D15 along with atezolizumab 1200 mg via intravenous (IV) infusion on D1 of each 21-day cycle.

If the 5 mg dose exceeds the MTD, then a 3 mg dose of entinostat (Dose Group -1) will be evaluated in the same manner. If the -1 dose level exceeds the MTD, then a 2 mg dose of entinostat (Dose Group -2) will be evaluated. Based on evaluation of the safety and tolerability data gathered during the dose determination phase together with data from other clinical trials, it may also be decided that accrual will take place at an alternate dose level or dosing schedule via a protocol amendment.

Patients who experience a DLT will be allowed to remain on study if they meet the following criteria; (1) the investigator believes it is appropriate for patients to remain on study (2) the event has resolved and no longer meets the definition of DLT and (3) the timeline for resolution falls within the guidelines for dose delays (Section 9.10).

Phase 2 (Expansion): The efficacy and safety of entinostat in combination with atezolizumab will be evaluated using the RP2D identified in the Dose Determination Phase. In this randomized, placebo-controlled, double-blind study phase, 70 patients will be randomized in a 1:1 fashion to atezolizumab + entinostat versus atezolizumab + placebo. The randomization will be stratified by geographic location (US vs. rest of world).

Patients will follow the same schedule of study visits and assessments as specified in the Dose Determination phase. The exception is the C2D15 tumor tissue core biopsy. While this was optional in the Dose Determination phase, it is mandatory in the Expansion Phase until 20 samples are obtained. If the data learned from those first 20 samples is deemed informative, this procedure may become mandatory for the remainder of the patients enrolled in this phase.

Following the enrollment and completion of Cycle 1 of the first 20 patients in this study phase, cumulative study safety data for all study patients will be reviewed by a Data Safety Monitoring Board (DSMB). The development of serious adverse events will be assessed by the Medical Monitor and DSMB on a continuous basis. At the first DSMB meeting, the DSMB members will confirm which SAEs they need to see real time or at time of DSMB meetings only. Unless the DSMB wishes to suspend enrollment during the review of the safety data for the first 20 patients, enrollment will continue during the data review process.

6.2 Number of Centers

Up to approximately 50 international study centers are planned to be recruited for participation in this study. Study centers that do not enroll at least 1 patient within 3 months of study center initiation may be subject to closure in consultation with the Sponsor.

6.3 Number of Patients

Phase 1b Dose Determination Phase: Up to 18 patients may be enrolled. In this phase, up to 3 doses of entinostat will be explored in a standard “3+3” Phase 1 dose finding scheme. Six patients will need to be treated in a dose level for it to be considered MTD or the RP2D. Entinostat dosing will start at 5 mg po weekly and then decrease to 3 mg weekly in the case that the 5 mg weekly dose leads to ≥ 2 DLTs. It will again be de-escalated to 2 mg weekly should the 3 mg weekly dose lead to ≥ 2 DLTs. Each patient will be counted in only 1 dose cohort. Thus, the total number of patients to be enrolled in the Dose Determination Phase is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose de-escalations required to achieve the MTD.

Note: The patients who discontinued the study for reasons other than study drug related toxicities before completing Cycle 1 may be replaced.

In the Phase 2 Expansion Phase, a total of 70 TNBC patients are planned to be enrolled for evaluation (35 patients per arm). Note: It is anticipated that the number of patients who will drop out of the study without PFS failure beforehand will be low (expected to not exceed 2–3%). Depending on the actual number of such dropouts, the number of patients accrued may be increased by 6–10 additional patients to accommodate for a higher-than-expected number of dropouts.

6.4 Estimated Study Duration

The estimated duration of study enrollment is approximately 15 months; 6 months for the Phase 1b and 9 months for the Phase 2. Patients may continue study treatment until unequivocal progressive disease, intolerable toxicity or meets one of the study withdrawal criteria (Protocol Section 11). Patients will be followed for overall survival until the Sponsor terminates the trial.

7. PATIENT ELIGIBILITY

7.1 Inclusion Criteria

Patients meeting all of the following criteria are considered eligible to participate in the study:

1. Females aged 18 years or older on the day written informed consent is given.
2. Has histologically or cytologically confirmed triple negative breast adenocarcinoma that is either metastatic (stage IV of the TNM classification) or locally recurrent and not amenable to local curative treatment. TNBC diagnosis should be based on local laboratory ER/PgR/HER-2 tests and will be defined as HER2 negativity (IHC 0-1 and/or ISH non-amplification) and ER and PgR negativity (<1%). Disease must also be amenable to core biopsy (image-guided if applicable) at enrollment and for certain cohorts as described in the protocol, at least once during study treatment.
3. Evidence of measurable (according to RECIST version 1.1) locally recurrent or metastatic disease based on imaging studies (e.g., CT, MRI) within 28 days before enrollment/randomization.
4. Has received at least 1, but no more than 2, prior lines of systemic therapy for locally recurrent and/or metastatic disease
5. If patient has a history of treated asymptomatic CNS metastases they are eligible, provided they meet all of the following criteria:
    - Patient has measurable disease outside CNS;
    - Patient does not have metastases to midbrain, pons, medulla or spinal cord;
    - Patient is not on corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed);
    - Patient has not had whole-brain radiation within 6 weeks prior to study enrollment;
    - Patient has stable CNS disease as demonstrated by at least 4 weeks of stability between the last intervention scan and the study screening scan
6. ECOG performance status of 0 or 1.
7. Has the following laboratory parameters within 21 days of enrollment:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[1] creatinine clearance (CrCl) (glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5× the upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels >1.5× institutional ULN

System	Laboratory Value
Hepatic	
Total bilirubin	≤1.5×ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5×ULN
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5×ULN **OR** ≤5×ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[1] Creatinine clearance should be calculated per institutional standard.

8. If a female of childbearing potential, has a negative serum blood pregnancy test during screening and a negative pregnancy test (urine or serum) within 3 days prior to receiving the first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a second test is not required. Note: Women of childbearing potential (WoCP) are any women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation. Menopause is defined as any of the following:
    - Bilateral oophorectomy,
    - Age ≥ 60,
    - Age <60 and amenorrheic for ≥ 12 months in the absence of an alternative medical cause and FSH and estradiol in postmenopausal ranges. .

    Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. WoCP include women who have experienced menopause onset < 12 months prior to enrollment.
9. If a female of childbearing potential, willing to use 2 methods of birth control or willing to abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug.
10. Experienced resolution of toxic effect(s) of the most recent prior anti-cancer therapy to ≤Grade 1 (except alopecia or neuropathy). If patient underwent major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
11. Able to understand and give written informed consent and comply with study procedures.

7.2 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study participation:

1. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Medical Monitor.
2. Active autoimmune disease including active diverticulitis, symptomatic peptic ulcer disease, colitis, or inflammatory bowel disease that has required systemic treatment in past 2 years (i.e., with disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
3. Previously treated with a PD-1/PD-L1-blocking antibody (i.e., atezolizumab, nivolumab, pembrolizumab) or a histone deacetylase inhibitor (i.e., vorinostat, belinostat, romidepsin, panobinostat)
4. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator, including, but not limited to:
    - History of immune deficiencies or autoimmune disease (see Appendix 3 for complete list)
    - Myocardial infarction or arterial thromboembolic events within 6 months prior to enrollment or severe or unstable angina, New York Heart Association (NYHA) Class III (see Appendix I) or IV disease, or a QTc interval > 470 msec.
    - Uncontrolled hypertension or diabetes mellitus.
    - Another known malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia [CIN]/cervical carcinoma *in situ* or melanoma *in situ*). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years.
    - Active infection requiring systemic therapy.
    - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. (see inclusion criterion 5)
5. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.
6. Received a live vaccine within 30 days of the first dose of treatment (inactivated forms of influenza vaccinations can be given during influenza season only (approximately October to March in the Northern hemisphere and April to September in the Southern Hemisphere).
7. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study enrollment or who has not recovered (i.e., ≤Grade 1 at enrollment) from AEs due to mAb agents administered more than 4 weeks earlier.

8. Prior chemotherapy within 3 weeks, targeted small molecule therapy or radiation therapy within 2 weeks prior to study enrollment or who has not recovered (i.e., ≤Grade 1 at enrollment) from AEs due to a previously administered agent.

   Note: Patients with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.

9. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to the first dose of treatment.
10. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.
11. Currently receiving treatment with any other agent listed on the prohibited medication list (protocol section 9.12)
12. If female, is pregnant, breastfeeding, or expecting to conceive starting with the screening visit through 120 days after the last dose of study drug.
13. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
14. Known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative]). Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
15. Allergy to benzamide or inactive components of entinostat.
16. History of allergies to any active or inactive ingredients of atezolizumab.
17. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

8. PATIENT ENROLLMENT

Section 15.3 describes documentation required prior to the commencement of study enrollment.

The screening period for a particular patient commences on the date on which the patient signs the informed consent form. The consent form must be signed before any study-specific tests are performed.

In Phase 1b, after a patient has been screened and successfully fulfills all eligibility criteria, a site representative will send a registration/enrollment form to the appropriate TRIO representative. A patient identification (ID) number will be provided to the site and the patient will be created in the electronic data capture (EDC) system. The site will then enter complete screening data. Once the screening data have been manually reviewed by TRIO, and the eligibility confirmed, the site will be informed via form, that the patient is eligible to be enrolled into the study at a determined Entinostat dose. If the patient is not eligible, the site will again be informed, via form and asked to indicate screen failure into the EDC system. This patient ID must be used on all study documentation related to that patient.

In the Phase 2 portion of the study, an automated system will randomize the patient to one of the blinded study arms. Refer to the Study Manual for details on this procedure.

9. TREATMENT PROCEDURES

9.1 Study Drugs

The study drugs being studied in combination during this clinical trial are atezolizumab and entinostat. First Study treatment is to be administered within 3 business days of enrollment/randomization into the study.

The Investigator shall take responsibility for maintaining appropriate records and ensuring appropriate supply, storage, handling, distribution, and usage of study drug, in accordance with the protocol and any applicable laws and regulations.

9.2 Entinostat

9.2.1 Supply and Storage

Entinostat is a synthetic small molecule bearing the chemical name 3-Pyridylmethyl N-{4-[(2-aminophenyl)carbamoyl]benzyl}carbamate and the molecular formula $C_{21}H_{20}N_4O_3$, with a molecular weight of 376.41. Entinostat is classified as an antineoplastic agent, specifically functioning as an inhibitor of histone deacetylases that promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes that leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis.

Entinostat/placebo is an oral drug supplied by Syndax to the sites as pink to light red (1 mg) or yellow (5 mg) as polymorph B coated tablets. Each tablet contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate as inert fillers. The film coating consists of hypromellose, talc, titanium dioxide, and ferric oxide pigments (red and yellow) as colorants.

Entinostat/placebo is to be stored at controlled room temperature (15ºC to 25ºC / 59ºF to 77ºF) in a secure, locked storage area to which access is limited.

Entinostat/placebo is to be protected from light. Entinostat/placebo is not to be exposed to extremes of temperature (greater than 30ºC / 86°F or less than 5ºC / 41°F). The pharmacist will dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers.

Entinostat/placebo will be supplied to patients in bottles containing enough pills for a 3-week cycle, plus an additional dose in case tablets are lost.

Please refer to the Pharmacy Manual for complete details regarding supply, storage accountability and destruction Entinostat.

9.2.2 Dosing and Administration

All patients will self-administer entinostat/placebo PO once weekly on study days 1, 8 and 15 of each 21 day cycle. A new bottle of entinostat/placebo will be dispensed on day 1 of each cycle, regardless of the number of pills remaining in the bottle from the previous cycle.

On study days on which patients receive both entinostat/placebo and atezolizumab, entinostat/placebo is to be taken prior to atezolizumab.

Entinostat/placebo is to be taken on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal.

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

If entinostat/placebo is vomited, dosing should not be re-administered but instead the dose should be skipped.

9.2.2.1 Phase 1b

During the Phase 1b Dose Determination Phase, all patients will receive atezolizumab 1200 mg IV on D1 of each 21 day cycle. They will also receive entinostat orally weekly on days 1, 8 and 15 of each cycle at either 5 mg, 3 mg or 2 mg. Both drugs will be given in an open-label fashion.

Patients who discontinue from the study treatment for reasons other than study drug-related toxicity before completing C1 may be replaced (refer to section 9.4).

9.2.2.2 Phase 2

During the Phase 2 Dose Expansion Phase, all patients will receive atezolizumab 1200 mg IV on D1 of each 21 day cycle. They will also receive the RP2D of entinostat or matched placebo weekly on days 1, 8 and 15 or each cycle. Entinostat/placebo will be given in double blind fashion.

Any detected cumulative toxicity may require later dose reductions and/or other changes to the dosing schedule, as appropriate, including further refinement of the RP2D.

9.3 Atezolizumab

9.3.1 Supply and Storage

Atezolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Atezolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Atezolizumab drug product is provided in a single-use, 20-mL USP/PH. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. The atezolizumab drug product is formulated as 60 mg/mL of atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab is supplied by Syndax to the sites and is given intravenously.

9.3.2 Dosing and Administration

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion q3w.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes, otherwise it should be delivered over 60 (±15) minutes. The patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined no more than 60 minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Refer to the Pharmacy Manual for complete details regarding supply, storage, accountability, and destruction of Atezolizumab.

9.4 Study Drug(s) Accountability

The lot number(s) of the study drugs (entinostat and atezolizumab) received at the site are to be recorded on the Drug Accountability Log maintained by the pharmacist. Additional distribution and return information will also be recorded at the site.

Patient medication instructions and dosing diaries will be provided to the patient for purposes of recording entinostat/placebo self-administration.

9.5 Entinostat Compliance

Treatment compliance to entinostat will be assessed at the end of each cycle. Patients will complete a diary to document their weekly intakes. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at each visit. Site staff will perform accountability of the returned drug and will assess patient compliance. Site staff must ensure that the patient clearly understands the directions for self-medication and follows the schedule.

9.6 Dose-limiting Toxicity

In the Dose-Determination Phase, DLTs will be assessed during the DLT assessment window, which is defined as the first cycle of treatment. The DLT assessment window (Cycle 1) is the time period between C1D1 until C2D1 (expected to be 21 days after C1D1).

In addition, the total dose of entinostat received over the first two cycles has to be evaluated as it corresponds to one of the DLT criteria.

A patient will be considered DLT evaluable if she:

- Incurs an adverse event meeting DLT criteria during Cycle 1

  Or

- Completes Cycle 1 and receives the full dose of atezolizumab and all doses of entinostat during this cycle, without incurring a DLT. In case a patient would not begin Cycle 2 for reasons other than a DLT, she would be considered DLT evaluable if she receives all planned doses of entinostat and atezolizumab during cycle 1 and completes 7 days after C1D15 without incurring a DLT.

Patients who are not considered DLT evaluable may be replaced to complete a cohort.

DLT is defined as the occurrence of any of the following events within **the DLT Assessment window** that are considered by the Investigator to be at least possibly related to study drug:

- Grade 5 events
- Grade ≥ 4 neutropenia (ANC $< 500/\mu L$) lasting ≥ 7 days
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 4 thrombocytopenia lasting > 48 hours
- Grade ≥ 4 anemia
- Grade ≥ 4 rash (cont'd on next page)
- Grade ≥ 3 symptomatic hepatic toxicities that do not resolve to Grade ≤ 2 within 48 hours or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset with the following **exception**:
  - For patients with Grade 2 AST, ALT, and/or alkaline phosphatase abnormality at enrollment, an increase to $> 10\times$ the upper limit of normal (ULN) that does not resolve to Grade ≤ 2 within 48 hours (if symptomatic) or that does not resolve to Grade ≤ 1 within 3 weeks of onset (if asymptomatic) will be considered a DLT.
- Grade ≥ 3 non-hematologic, non-hepatic organ toxicity, with the following **exceptions:**

- Grade 3 immune-related adverse event that resolves to Grade ≤ 1 within 3 weeks of its onset
- Grade 3 nausea or vomiting that resolves to Grade ≤1 within 72 hours of appropriate supportive therapy
- Grade ≥3 fatigue that resolves to Grade ≤2 within 7 days
- Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤2 within 7 days
- Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤2 within 7 days with supportive care
- Grade ≥3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant
- Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormonal replacement
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Grade 3 infusion reaction that resolves within 6 hours to Grade ≤1

- Inability to receive all 3 doses of entinostat during the first cycle

In addition, the inability to receive greater than 60% of the planned entinostat dose during the first 2 cycles, will also be considered a DLT.

All DLTs will be reported on the AE eCRF in the EDC system within 24 hours. All DLTs will be considered adverse events of special interest for this protocol and will be reported to TRIO in an expedited manner. Please see Protocol Section 12.4 and also refer to the Adverse Event Reporting Procedures in the Study Manual.

Patients who experience a DLT will be allowed to remain on study if they meet the following criteria: (1) the investigator believes it is appropriate for patients to remain on study (2) the event has resolved and no longer meets the definition of DLT and (3) the timeline for resolution falls within the guidelines for dose delays (Section 9.10).

9.7 Maximum Tolerated Dose

MTD is defined as the highest dose level at which <33% of 6 patients experience DLT.

9.8 Recommended Phase 2 Dose

The RP2D will be equal to or less than the preliminary MTD. The RP2D will be determined in discussion with the Sponsor, Medical Monitor, and Dose Determination Phase Investigators. Additionally, observations related to immune correlates, and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D.

9.9 Treatment Duration

The duration of treatment for this study is expected to be 1 year. Patients may remain on study until unequivocal progressive disease, unacceptable toxicity, or another treatment withdrawal criteria is met per Protocol Section 11. Study patients with evidence of radiological progressive disease who meet the criteria set forth in Protocol Section 10.3.2 for "Treatment After Initial Radiological Progression", should continue treatment and be followed according to irRECIST as described in section 10.3.2. Any questions should be directed to the Medical Monitor.

If a patient permanently discontinues either study drug (entinostat/placebo or atezolizumab), the patient will be taken off study treatment and followed for progressive disease per protocol guidelines, or overall survival should progressive disease have been previously determined on study. Patients will receive standard of care outside the auspices of this study at the Investigator's discretion.

After discontinuation of study treatment, patients will complete an EOT visit within 7 days (+/- 3 days) after the last study drug dose and a Safety F/U visit 30 days (+/- 3 days) thereafter.

After completion of the 30-day Safety F/U visit, patients who have not experienced PD are to continue to undergo radiological assessments every 6 weeks until study week 36, and then every 9 weeks thereafter until progressive disease. The purpose of the post-treatment follow-up is to ascertain the duration of PFS for all patients in the study.

After they experience PD, surviving patients are to be contacted every 3-months for documentation of subsequent therapies and survival until closure of the study or patient death, whichever should occur first.

9.10 Dose Interruptions and Modifications

Although entinostat and atezolizumab have distinct toxicity profiles, they do share some AEs such as fatigue and nausea. There is also the possibility that 1 agent may potentiate the other and hence drug causality will not always be clear. In the event of uncertainty, dose reductions or delays will follow the most conservative approach (i.e., delays and/or dose reductions for both drugs) until resolution of the event, or the patient is taken off study. However, if the toxicity is clearly associated with only one of the study drugs, then the other study drug may be continued at the discretion of the study investigator in consultation with the Medical Monitor, until resolution of the event or the patient is taken off study.

Note: If a patient permanently discontinues either study drug (entinostat/placebo or atezolizumab), the patient will be taken off study treatment

No dose reductions will be performed for atezolizumab.

Guidance for entinostat delays and or dose reductions can be found in Protocol Section 9.10.1 . All dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined in the protocol on the basis of clinical judgment that is in the best interest of the subject. Such instances should be reported to the Medical Monitor. Expected AEs for each agent are summarized in Section 12.

9.10.1 Entinostat

In Phase 1b, dose delays, but not dose reductions will be allowed for entinostat during Cycle 1. If a dose reduction is required during Cycle 1, the patient will be taken off study. Dose delays for reasons other than toxicities definitely or possibly related to entinostat should be avoided as much as possible during Cycle 1.

In Phase 2, both dose delays and dose reductions will be allowed as described below. Once the entinostat dose is reduced, it cannot be re-escalated.

9.10.1.1 Non-hematologic Toxicity at Least Possibly Related to Entinostat

The rules outlined in Table 9-1 are to be followed for the management of non-hematologic toxicities that are definitely or possibly due to entinostat alone, with toxicities graded by the Investigator according to the NCI, CTCAE, version 4.03. Note: No dose reduction is allowed during the first study treatment cycle in phase 1b.

Table 9-1 Non-hematologic Toxicity: Dose Modifications for Entinostat

Toxicity	Dose modifications
Grade 4	Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline under the following directions. 1. If recovered within 4 weeks of onset (ie: ≤3 missed doses) , resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, discontinue study treatment 2. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline under the following directions: 1 If recovered by next scheduled dose, resume study drug at prior dose. If not recovered by next scheduled dose, continue to hold the dose. 2 If recovered within 2-4 weeks (i.e. missed 3 or less doses) resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. • If receiving 2 mg, discontinue study treatment. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the **same** Grade 3 toxicity despite dose reduction	Administer symptomatic remedies / start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold[1] dose until recovery to Grade 1 or baseline. 1. If recovered within the next 2 scheduled doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg 2. If the **same** ≥Grade 3 event **recurs** (i.e., 3 occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.
≤Grade 2	Administer symptomatic remedies / start prophylaxis. Dosing of study drug may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.[1] • If toxicity resolves, resume entinostat at the original dose.

[1] *If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.*

9.10.1.2 Hematologic Toxicity at Least Possibly Related to Entinostat

The guidelines in Table 9-2 will be followed for determining the timing of cycles based on hematologic status at the time of planned dosing. Note: No dose reduction is allowed during the first study treatment cycle during phase 1b.

Table 9-2 Hematologic Toxicity: Dose Modification for Entinostat

Toxicity	Dose modifications
≥Grade 3 neutropenia, ≥Grade 3 uncomplicated thrombocytopenia, or Grade 2 complicated thrombocytopenia	Administer symptomatic remedies/ start prophylaxis. Hold dose[1] until recovery to Grade 1 or study baseline using the following directions: 1. If recovered by next scheduled dose, resume study drug at prior dose. If not recovered by next scheduled dose, hold the dose. 2. If recovered within the next 2-4 weeks (i.e. missed 3 or less doses) resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. • If receiving 2 mg, permanently discontinue study drug. 3. If not recovered within 4 weeks (i.e. 4 doses missed), permanently discontinue study drug.
Recurrence of the **same** hematologic toxicity	Administer symptomatic remedies/ start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold[1] dose until recovery to Grade 1 or baseline. 1. If recovered within the next 2 scheduled doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg 2. If the **same** ≥Grade 3 event **recurs** (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.

1 If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.

9.10.2 Atezolizumab

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

Patients may temporarily suspend study treatment for up to 84 days beyond the last dose if they experience adverse events that require atezolizumab to be withheld. If atezolizumab is withheld because of atezolizumab related adverse events for >84 days beyond the last dose, then the patient will be discontinued from study treatment and will be followed up for safety and efficacy per protocol.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold of >84 days, and entinostat has been administered per protocol during this time, study drug may be restarted only with the approval of the Medical Monitor.

As discussed in Protocol Section 9.12, systemic corticosteroids should be used to treat immune mediated toxicities related to atezolizumab. If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be held for additional time beyond 84 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on an agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor .

9.11 Concomitant Therapy

All concomitant treatments and therapies, or medication, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids, administered during the 30 days preceding the screening study visit must be reported in the electronic case report form (eCRF). If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF. The generic name of the drug (or trade name for combination drugs) must be specified along with the route of administration, indication, and duration of treatment.

Throughout the study, the Investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, such as potassium and phosphorus supplements and antiemetics, with the exception of those listed in Section 9.12.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor. Patients must notify the Investigator of all concomitant medications taken through completion of the study (30 day follow-up safety visit).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (Section 9.12). If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study drug will be required. The Investigator should discuss any questions regarding this with the Medical Monitor.

The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study drug requires the mutual agreement of the investigator, the Medical Monitor and the patient.

9.12 Prohibited Medication

The following medications are excluded while the patient is receiving study treatment:

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- Any additional investigational or commercial anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy, will not be allowed, even if utilized as treatment of non-cancer indications.
- Prophylactic use of hematopoietic colony stimulating factors are not allowed during the Phase 1b, but can be used per investigator discretion during other parts of the study.
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the Medical Monitor. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered progressive disease and the subject should be removed from study treatment. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
- RANKL inhibitor (denosumab): patients who are receiving denosumab prior to randomization must be willing and eligible to receive a bisphosphonate instead while on study
- Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the 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, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed
- Any live, attenuated vaccine (e.g., FluMist®) while the patient is receiving atezolizumab and for a period of 90 days after the discontinuation of atezolizumab

Influenza vaccinations (inactivated forms only) should be given during influenza season only (approximately October to March in the Northern hemisphere and April to September in the Southern Hemisphere).

Systemic corticosteroids and anti–TNF-α agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab. If feasible, alternatives to these agents should be considered. Systemic corticosteroids may be administered at the discretion of the treating physician in consultation with the Medical Monitor at doses no greater than 10 mg prednisone or for no longer than 7 consecutive days if at higher doses, to treat acute conditions other than immune-mediated toxicity related to study drug. The use of physiologic doses of corticosteroids for prolonged periods may be approved in consultation with the Medical Monitor. Inhaled steroids are allowed for management of asthma or other chronic disorders, as prescribed.

Patients should not receive other immunomodulatory agents for 10 weeks after the last dose of atezolizumab.

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study, unless as otherwise noted. Patients may receive other medications that the Investigator deems to be medically necessary.

The exclusion criteria (Section 7.2) describe other medications that are prohibited in this study.

9.13 Medications to be Avoided During the Study

Concomitant use of the drugs below with entinostat should be avoided during the study:

- Sensitive substrates of CYP enzymes listed in Appendix 2
- Drugs that are known to inhibit or induce P-gp (see Appendix 2)

Should the use of these medications be required, the Medical Monitor must be consulted for guidance.

9.14 Management for Atezolizumab-Specific Adverse Events

Toxicities associated with, 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 determine 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, mycophenolate, or TNF-α inhibitors.

The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

For the management of other adverse events associated with the atezolizumab not provided below, refer to the Atezolizumab IB.

9.14.1 Pulmonary Events

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

All pulmonary events should be evaluated thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. by the following means:

Measurement of oxygen saturation (i.e., arterial blood gas)

Bronchoscopy with bronchoalveolar lavage and biopsy

Pulmonary function tests (diffusion capacity of the lung for carbon monoxide [DL_{CO}])

Pulmonary function testing with a pulmonary embolism protocol

Table 9-3 Management Guidelines for Pulmonary Events, Including Pneumonitis

Severity	Management
Grade 1	• Continue atezolizumab with close monitoring • Re-evaluate on serial imaging • Consider pulmonary consultation
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Pulmonary and infectious disease specialists consultation and consider bronchoscopy or bronchoscopic alveolar lavage (BAL) • Start treatment with 1–2 mg/kg/day oral prednisone or equivalent • When improves to Grade 0 or Grade 1, then taper steroids over ≥ 1 month.Atezolizumab may be resumed if the event improves to Grade 0 or Grade 1 [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • Treat as Grades 3–4 for recurrent events
Grades 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Bronchoscopy/BAL is recommended • Start treatment with 1-2 mg/kg/day oral prednisone or equivalent • Taper steroids over ≥ 1 month after symptoms improve to Grade 0 or Grade 1 • If not improving within 48 hoursafter initiating corticosteroids, consider adding an immunosuppressive agent

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

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

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

9.14.2 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

While in 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 LFTs increase, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriateImaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti–smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Table 9-4 Management Guidelines for Hepatic Events

Severity	Management
Grade 1	• Continue atezolizumab • Continue LFT monitoring until values resolve to within normal limits
Grade 2	**All Events:** • Monitor LFTs at least twice a week until return to baseline values **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 0 or Grade 1, resume atezolizumab [b] • If corticosteroids have been started, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • If persists > 5–7 days: withhold therapy and start 60 mg prednisone or equivalent per day; when LFTs are ≤ Grade 1, taper steroids over ≥ 1 month, resume therapy if the event improves to Grade 0 or Grade 1 within 12 weeks and systemic steroid dose is ≤ 10mg oral prednisone equivalent per day.
Grades 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor. c • Consider gastrointestinal (GI) specialist consult and liver biopsy to establish etiology of hepatic injury • Start 1-2 mg/kg/day oral prednisone or equivalent • If event does not improve within 48 hours after initiation of corticosteroids, consider adding an immunosuppressive agent • Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1

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

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

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

9.14.3 Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. If the event is of significant duration or magnitude or is 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 for confirmation of the diagnosis of colitis.

Perform laboratory tests to rule out alternate etiology (i.e., WBCs and stool calprotectin).

Table 9-5 Management Guidelines for Gastrointestinal Events (Diarrhea/Colitis)

Severity	Management
Grade 1	• Continue atezolizumab • Symptomatic treatment • Endoscopy is recommended if symptoms persist for greater than 7 days • Close monitoring
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Symptomatic treatment • GI consultation recommended • If persists >5 days or recurs start oral prednisone 1-2 mg/kg/day or equivalent • Taper steroids over ≥ 1 month when symptoms improve to Grade 0 or Grade 1 • may be resumed if the event improves to Grade 0 or Grade 1[b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • GI referral and confirmation biopsy • Start treatment with IV steroids 1–2 mg/kg/day methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent after improvement • When improves to Grade 0 or Grade 1, then taper steroids over ≥ 1 month. • may be resumed if event improves to Grade 0 or Grade 1[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • GI referral and confirmation biopsy • Start treatment with IV steroids 1–2 mg/kg/day methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent after improvement • When patient's diarrhea or colitis improves to Grade 0 or Grade 1, then taper steroids over $\geq$ 1 month • If not improving within 48 hours of initiating corticosteroids, consider adding an a immunosuppressive agent

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor

9.14.4 .Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus and pituitary disorders have been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be obtained 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 adrenal insufficiency from primary pituitary insufficiency.

Table 9-6 Management Guidelines for Endocrine Events

Severity/Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab • Start thyroid replacement hormone • Monitor TSH weekly
Symptomatic hypothyroidism	• Withhold atezolizumab. • Start thyroid replacement hormone • Monitor TSH weekly • Consider referral to an endocrinologist. • Restart atezolizumab when symptoms are controlled andthyroid function is improving
Asymptomatic hyperthyroidism	If serum TSH $\geq$ 0.1 mU/L and $<$ 0.5mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks TSH $<$ 0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism
Symptomatic hyperthyroidism	• Withhold atezolizumab • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider referral to an endocrinologist • Restart atezolizumab when symptoms are controlled by thyroid replacement and thyroid function is improving • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to endocrinologist • Perform appropriate imaging • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 0 or Grade 1 and patient is stable on replacement therapy, resume atezolizumab [b] • If event does not resolve to Grade 0 or Grade 1 or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Hyperglycemia Grade 1 or 2	• Continue atezolizumab • Start treatment with insulin if needed • Monitor for glucose control

Table 9-6 Management Guidelines for Endocrine Events	
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab • Start treatment with insulin • Monitor for glucose control • Resume atezolizumab when symptoms resolve and glucose levels are stable
Hypophysitis pan-hypopituitarism), Grade 2-3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to endocrinologist • Perform brain MRI (pituitary protocol) • Start 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 [a] • Initiate hormone replacement therapy if clinically indicated • If event resolves to Grade 0 or Grade 1, resume atezolizumab [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • For recurrent hypophysitis, treat as a Grade 4 event
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol) • Start 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 [a] • Initiate hormone replacement therapy if clinically indicated

IV = intravenous; TSH = thyroid stimulating hormone; MRI = magnetic resonance imaging;

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

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

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

9.14.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).

Table 9-7 Management Guidelines for Ocular Events

Severity	Management
Grade 1	• Continue atezolizumab • Evaluation by an ophthalmologist is strongly recommended • Treat with topical corticosteroid eye drops and topical immunosuppressive therapy • If symptoms persist, treat as a Grade 2 event
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Patient referral to ophthalmologist is strongly recommended • Start treatment with topical corticosteroid eye drops and topical immunosuppressive therapy • If event resolves to Grade 0 or Grade 1, resume atezolizumab [b] • If event does not resolve to Grade 0 or Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to ophthalmologist • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 0 or Grade 1, taper corticosteroids over ≥ 1 month

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

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

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

9.14.6 Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related 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 pre-existing 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.

Table 9-8 Management Guidelines for Immune-Related Myocarditis

Severity	Management
Grade 1	• Refer patient to cardiologist • Start treatment as per institutional guidelines
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement [a] • If event resolves to Grade 0 or Grade 1, resume atezolizumab [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 0 or Grade 1, taper corticosteroids over ≥ 1 month

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device; 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

9.14.7 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of other immuno-modulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Table 9-9 Management Guidelines for Pancreatitis

Pancreatic Event	Severity	Management
Amylase and /or lipase elevation	Grade 2	• Continue atezolizumab • Monitor amylase/lipase weekly • Consider oral prednisone 10 mg daily or equivalent for prolonged elevation (e.g., more than 3 weeks)
Amylase and /or lipase elevation	Grades 3 and 4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Consult a gastroenterologist • Monitor amylase/lipase every other day • Consider oral prednisone 1-2 mg/kg/day or equivalent if no improvement • Atezolizumab may be resumed if the event resolves to Grade 0 or Grade 1 [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • Permanently discontinue atezolizumab for recurrent events and notify the Medical Monitor [c]
Immune-related pancreatitis	Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Consult a gastroenterologist • Start treatment with 1-2 mg/kg/day IV methylprednisone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent when symptoms improve • Atezolizumab may be resumed if the event improves to Grade 0 or Grade 1 If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • Permanently discontinue atezolizumab for recurrent events and notify the Medical Monitor [c]
Immune-related pancreatitis	Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to gastrointestinal specialist • Start 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 0 or Grade 1, taper corticosteroids over ≥ 1 month.

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

9.14.8 Infusion-Related Events

No premedication is indicated for the administration of atezolizumab in Cycle 1. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis.

Table 9-10 Management Guidelines for Infusion-Related Reactions

Severity	Management
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 tolerated, the infusion rate may then be increased to the original rate
Grade 2	• Interrupt atezolizumab infusion • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) • 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 antihistamine, anti-pyretics, and/or analgesics and monitor closely for IRRs
Grades 3–4	• Stop infusion • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) • Permanently discontinue atezolizumab and contact Medical Monitor [a]

IRR = infusion-related reactions; IV = intravenous.

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

Table 9-11 Management Guidelines for Pancreatitis

Pancreatic Event	Severity	Management
Amylase and /or lipase elevation	Grade 2	• Continue atezolizumab • Monitor amylase/lipase weekly • Consider oral prednisone 10 mg daily or equivalent for prolonged elevation (e.g., more than 3 weeks)

Amylase and /or lipase elevation	Grades 3 and 4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Consult a gastroenterologist • Monitor amylase/lipase every other day • Consider oral prednisone 1-2 mg/kg/day or equivalent if no improvement • When lab abnormalities return to Grade 0 or Grade 1, then taper steroids over ≥ 1 monthAtezolizumab may be resumed if the event resolves to Grade 0 or Grade 1 [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • Permanently discontinue atezolizumab for recurrent events and notify the Medical Monitor [c]
Immune-related pancreatitis	Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Consult a gastroenterologist • Start treatment with 1-2 mg/kg/day IV methylprednisone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent when symptoms improve • Atezolizumab may be resumed if the event improves to Grade 0 or Grade 1 If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • Permanently discontinue atezolizumab for recurrent events and notify the Medical Monitor [c]
Immune-related pancreatitis	Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to gastrointestinal specialist • Start 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 0 or Grade 1, taper corticosteroids over ≥ 1 month.

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

9.14.9 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Table 9-12 Management Guidelines for Immune-Mediated Dermatologic Events

Severity	Management
Grade 1	• Continue atezolizumab • Consider topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines)
Grade 2	• Continue atezolizumab • Consider dermatologist referral • Administer topical corticosteroids • Consider higher potency topical corticosteroids if event does not improve
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Consult a dermatologist • Start treatment with oral prednisone 10 mg/day or equivalent. If event unresolved after 48–72 hours, administer oral prednisone 1-2 mg/kg/day or equivalent • Restart atezolizumab if event resolves to Grade 0 or Grade 1 [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]

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

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

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

9.14.10 Neurological Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor

neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.

Table 9-13 Management Guidelines for Neurologic Disorders

Neurologic Disorder	Severity	Management
Myasthenia Gravis and Guillain-Barré syndrome	All grades	• Permanently discontinue atezolizumab and contact the Medical Monitor [c] • Refer patient to a neurologist • Start treatment as per institutional guidelines Consider initiation of 1-2 mg/kg/day oral of IV prednisone or equivalent
Immune-related neuropathy	Grade 1	• Continue atezolizumab. • Investigate etiology
Immune-related neuropathy	Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Investigate etiology • Treatment should be as per institutional guidelines • If event resolves to Grade 0 or Grade 1, resume atezolizumab [b] • If event does not resolve to Grade 0 or Grade 1 while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Immune-related neuropathy	Grades 3–4	• Permanently discontinue atezolizumab and contact the Medical Monitor [c] • Start treatment as per institutional guidelines •

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

9.14.11 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related 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 9-13.

Table 9-14 Management Guidelines for Immune-Related Meningoencephalitis

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

IV = intravenous.

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

9.14.12 Systemic Immune Activation

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

9.15 Diet/Activity/Other Considerations

9.15.1 Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

9.15.2 Contraception

Women of childbearing potential must agreement to remain abstinent (refrain from heterosexual intercourse) or use 2 contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 120 days after the last dose of study treatment.

A woman is considered to be of childbearing potential if she is between menarche and menopause and has not been permanently or surgically sterilized and is capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. This definition also includes women who have experienced menopause onset < 12 months prior to enrollment.

Examples of single contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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.

Patients should be informed that taking the study dug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and for at least 120 days after the last dose of study treatment. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.15.3 Study Drug Use in Pregnancy

If a patient inadvertently becomes pregnant while on study drug, the patient will immediately be removed from study treatment. The site will contact the patient at least monthly and document

the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to TRIO without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. See Section 12.4.1 for information regarding reporting a pregnancy.

9.15.4 Study Drug Use in Nursing Women

It is unknown whether study drug is excreted in human milk. Since many drugs are secreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

10. STUDY TESTS AND OBSERVATIONS

After provision of written informed consent, patients will be screened for study eligibility within 21 days before study enrollment. Patients who are determined to be eligible based on screening assessments and who are enrolled, **must begin treatment (C1D1) with entinostat/placebo in combination with atezolizumab within 3 business days of the date of enrollment/randomization.**

A cycle is 21 days in length. Patients will attend study center visits and undergo study evaluations on C1D1, C1D8, and C1D15; D1 and D15 of C2; and on D1 of each cycle thereafter.

Patients will have radiological disease assessments during screening and then during treatment and follow-up every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) through week 36 and then every 9 weeks (+/- 3 days) thereafter until unequivocal progressive disease. This schedule is to be followed both during study treatment and following discontinuation of study treatment in the absence of progressive disease.

After discontinuation of study treatment, patients will complete an EOT visit within 7 days (+/- 3 days) after the last study drug dose and a Safety Follow-up visit 30 days (+/- 3 days) thereafter. After completion of the 30-day Safety F/U visit, patients who have not experienced PD are to continue to undergo radiological assessments every 6 weeks through week 36 and then every 9 weeks thereafter until unequivocal progressive disease. The purpose of the post-treatment follow-up is to ascertain the duration of PFS for all patients in the study. After progressive disease, surviving patients are to be followed every 3-months for documentation of subsequent therapy and survival until closure of the study or death.

Protocol-required tests, observations, and procedures are summarized in Table 1-1.

10.1 Screening Assessments

All patients must provide written informed consent before the performance of any study-related procedures.

10.1.1 Demographics

Patient demographics, including age, race, and ethnicity, are to be documented during screening.

10.1.2 Medical History

A complete medical history is to be documented during screening and updated prior to administration of the first study drug dose.

The medical history is to include cancer history, including date of and stage at diagnosis, method of diagnosis, and all previous treatments, including radiation therapy, and response to such treatment. It should also include any medical condition that might complicate the patient's disease or affect the treatment outcome.

10.1.3 Pregnancy Testing

For females of child-bearing potential, a serum pregnancy test is required and must be performed during screening and a urine test within 3 days before the first study drug dose if the serum test is performed more than 3 days before the first study drug dose. Results must be available and confirmed to be negative prior to study drug administration. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

10.2 Safety Assessments

10.2.1 Physical Examination

A complete physical examination will be conducted for all patients during screening; at enrollment; and at the EOT (within 7 days post-last dose) and Safety F/U (30 days (+/-3 days) thereafter) visits. If the screening complete physical examination was performed within 7 days of enrollment, then a symptom-directed physical examination may be performed at C1D1.

Symptom-directed physical examinations will be performed for all patients on D1, D8, and D15 of C1; D1 and D15 of C2; and on D1 of each subsequent cycle.

10.2.2 Electrocardiograms

All patients will undergo a 12-lead ECG during screening; pre-dose (i.e., before entinostat and atezolizumab) on C3D1, and then every 3 cycles thereafter. A 12-lead ECG also is to be repeated as clinically indicated during treatment and again at the EOT visit (within 7 days post-last dose).

ECGs will be recorded after the patient has rested in a supine position for at least 10 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs when they are collected.

10.2.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse (beats per minute), respiration rate (breaths per minute), and temperature, are to be measured during screening, on D1 of each treatment cycle, at the EOT (7 days post-last dose) and the Safety F/U visits.

Measurements are to be made after the patient has been resting in a supine position for a minimum of 5 minutes.

Blood pressure and pulse will be measured using a blood pressure recording device with an appropriately sized cuff. The units (°F or °C) and mode of temperature recording will be documented (e.g., oral, axillary); the same units and mode should be used for a patient across all measurements. Height will be collected at the screening visit only.

10.2.4 Weight

Weight is to be measured during screening, on D1 of each treatment cycle, at the EOT and the Safety F/U visits.

10.2.5 ECOG Performance Status

ECOG performance status is to be assessed during screening, on D1 of each treatment cycle, and at the EOT and Safety F/U visits. It should also be measured if there is any indication of fluid retention.

The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 10-1.

Table 10-1 Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores

ECOG[1]		Karnofsky[2]	
Score	**Criterion**	**%**	**Criterion**
0	Normal activity	100	Normal; no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms but ambulatory	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self; unable to carry on normal activity or do active work
2	In bed <50% of time	60	Requires occasional assistance but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of time	40	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization is indicated though death is not imminent
4	100% bedridden	20	Very sick; hospitalization is necessary
		10	Moribund; fatal processes progressing rapidly
5	Dead	0	Dead

1 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

2 Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

10.2.6 Clinical Laboratory Tests

Blood samples for hematology and clinical chemistries are to be collected during screening, on D1, D8 and D15 of C1; on D1 and D15 of C2; on D1 of each subsequent treatment cycle; and at the EOT visit. If screening hematology and clinical chemistry tests are performed within 7 days of enrollment, they need not be repeated at C1D1 unless clinically indicated.

The following analytes are to be measured:

Hematology

White blood cell count (WBC) with differential	Hemoglobin
Red blood cell count (RBC)	Hematocrit
Platelet count	Coagulation studies, including PT or INR and aPTT (screening only)

Clinical Chemistries

ALT	AST
Alkaline phosphatase	Albumin
Total bilirubin	Blood urea nitrogen (BUN)
Calcium	Creatinine
Sodium	Potassium
Chloride	Bicarbonate
Glucose	Lactic dehydrogenase
Phosphorus	Total Protein
Uric acid	Magnesium and TSH (screening only, unless clinically indicated)

In addition to the scheduled assessments, clinical laboratory evaluations are to be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Laboratory abnormalities that are considered by the Investigator to be clinically significant for a particular patient are to be reported as AEs.

10.2.7 Adverse Events

AEs, as defined in Section 12.2.1, are to be documented from the time of informed consent through 30 days post-last dose, with the exception of AESIs with atezolizumab, which must be

documented through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier.

10.3 Efficacy Assessments

With the exception of OS, all efficacy endpoints in this trial (including the primary endpoint in Phase 2) are linked to the tumor response assessments and therefore the importance of timely and complete disease assessments in this study cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

The schedule of tumor burden assessments should be fixed according to the calendar, regardless of treatment interruptions. Tumor burden assessments will be performed until progressive disease as per RECIST 1.1 and irRECIST regardless of the discontinuation of study treatment or the start of a subsequent anticancer therapy. Patients with radiographic progression only, as defined by RECIST 1.1 should continue on study treatment until unequivocal progressive disease is determined as defined by irRECIST, at the discretion of the investigator.

The same method of assessment and the same technique used for study screening (CT scan or MRI) to characterize each lesion must be used at each subsequent post-screening assessment. Post-screening scans and the corresponding overall tumor assessment (according to RECIST and irRECIST) should be done at the next visit after the scans are performed and prior to indicating the subsequent cycle, to rule out progressive disease that would warrant study treatment discontinuation.

10.3.1 Tumor Measurements and Disease Response Assessment

10.3.1.1 Tumor Measurement and Assessment

Initial tumor imaging at screening must be performed within 28 days prior to initial study drug dosing (C1D1). (Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to C1D1 and can be assessed by the central imaging vendor.) Patients will have radiological disease assessments performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during study treatment through week 36 or until progressive disease. If progressive disease has not

occurred by week 36, radiological assessments will be then be done every 9 weeks (+/-3 days) until progressive disease. If a patient comes off study for reasons other than progressive disease, radiological assessments will continue on this same study schedule until progressive disease is unequivocally documented. Images should be kept to the calendar schedule and not be delayed for delays in cycles or study drug administration. Disease response in target and non-target lesions will be assessed locally by the Investigator using RECIST 1.1 and irRECIST.

Measurable Disease

To be eligible for study participation, all patients must have documented measurable disease per RECIST 1.1 that has been radiologically documented within 28 days prior to initiating study drug treatment, defined as follows:

At least 1 measurable lesion:

- ≥10 mm in longest diameter on an axial image by CT scan or MRI with ≤ 5 mm reconstruction interval
    - If slice thickness is greater than 5 mm, longest diameter must be at least 2 times the thickness
- ≥20 mm longest diameter by chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferred, even without contrast.
- Lymph nodes ≥ 15 mm in short axis on CT scan (CT slice thickness of ≤ 5 mm)

If there is only 1 measurable lesion and it is located in previously irradiated field, it must have demonstrated progression according to RECIST 1.1.

Non-measurable Lesions

Non-measurable lesions are defined per RECIST 1.1 as the following and should be captured and followed accordingly and within the eCRF according the eCRF guidelines.

- Masses < 10 mm
- Lymph nodes ≥10 to <15 mm in short axis
- Leptomeningeal disease
- Ascites, pleural or pericardial effusion
- Inflammatory breast disease (cont'd on next page)
- Lymphangitic involvement of skin or lung

- Abdominal mases or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques
- Blastic bone lesions
- Both benign and equivocal ("cannot exclude") findings should not be included

Target versus non-target

- Target: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at screening. Target lesions are to be selected on the basis of their size (i.e., those with the longest diameter) and suitability for accurate repeated measurement. The sum of the diameters for all target lesions is to be calculated and recorded on the eCRF as the sum of the longest diameters.
- Non-target: all other lesions not classified as target lesions (or sites of disease) are to be identified as non-target lesions and are to be recorded on the eCRF. Measurement of non-target lesions is not required.

10.3.1.2 Scan Procedures

Contrast-enhanced CT scans of chest, abdomen, and, as clinically indicated, pelvis are preferred for evaluation of disease status for this study; however, a contrast-enhanced MRI can also be performed if a patient has or develops allergy to iodinated contrast agents. The imaging modality used at screening should continue for all images during study participation, unless clinically contra-indicated.

Positron emission tomography (PET) alone will not be acceptable as part of the imaging to be performed for this study. If PET is performed, the Investigator should not remove any patient based on PET alone, as there can be false positives. If he/she thinks a patient has progressed via PET, it must be confirmed with a CT/MRI.

If a combined 18F-deoxyglucose (FDG) PET-CT scan is performed, the CT portion of that examination should not be substituted for the dedicated CT examinations required by this protocol for tumor measurements **unless** the study center can document that the CT performed as part of the FDG PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

CT Scan Procedures

Study centers must acquire and submit CT scans according to the parameters below:

- Use consistent scan parameters (spacing, thickness, field of view, etc.) for all assessments. Any alternate imaging or parameter variation from the protocol should be noted.
- If a patient develops hypersensitivity to the iodinated contrast medium while on study, it is acceptable to perform chest CT scans without contrast. In addition, a contrast-enhanced MRI scan according to the parameters described in the MRI section must be performed for the remainder of the required anatomy.
- The patient should be given oral contrast (as either positive [e.g., barium or Gastrografin] or negative [e.g., water or saline] contrast media, according to site standard of care) prior to the examination to allow for sufficient bowel opacification.
- Non-ionic iodinated IV contrast with a minimum of 320 mg iodine/mL should be used for this study. Contrast agent volume should be according to the package insert. The same contrast agent with the same concentration should be used throughout the study.

MRI Scan Procedures

- If IV contrast is medically contraindicated during the study, a dynamic contrast-enhanced MRI is an acceptable alternative to CT scans of the abdomen and pelvis.
- MRI must be performed using either 1.5T or 3.0T scanner. A change in scanner field strength is not allowed for an individual patient while on study (e.g., if a patient has a C2 MRI scan at 3.0T, all subsequent scans must be performed at 3.0T).
- MRI scans should use optimized parameters to decrease motion artifact and maximize signal-to-noise ratio and resolution. Breath-hold imaging, fast-scanning techniques, and gadolinium should be used to maximize lesion identification. Note: A non-contrast CT scan of the chest or digital chest X-ray must be acquired in addition to the MRI of the abdomen and, as applicable, pelvis.
- The patient must undergo scanning with approved extracellular contrast media only (e.g., Magnevist, Dataram, Omniscan).

- The same equipment, field strength, sequences, scanning parameters, positioning, angulation, timing, field of view, and slice thickness should be utilized for all examinations acquired both pre- and post-contrast for a given patient over the course of the study.

10.3.1.3 Disease Response Assessment Criteria

Patients will have radiological disease assessments performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during study treatment through week 36 or until unequivocal progressive disease. If progressive disease has not occurred by week 36, radiological assessments will be then be done every 9 weeks (+/-3 days) until unequivocal progressive disease. Images should be kept to the calendar schedule and not be delayed for missed study drug administration.

Partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan if on a 6 week schedule, whichever is clinically indicated.

In subjects who discontinue study therapy without documented unequivocal progressive disease, every effort should be made to continue monitoring their disease status by tumor imaging every 6 weeks until (1) unequivocal progressive disease (2) death, or (3) the end of the study, whichever occurs first. All scans will be submitted (electronically whenever possible) to a central core radiologic laboratory within 3 days of being performed, where they will immediately be reviewed for readability. The lab will contact the site should any issues or questions arise.

Disease progression is determined locally, not by the central core radiologic lab. Scans from patients who were determined by the Investigator to have a response to treatment (CR or PR) will be reviewed by the core radiologic laboratory to confirm response The lab will collect and hold all scans should the sponsor decide to have them read to confirm PFS outcomes.

Scans from non-responders may also be reviewed by the core radiologic laboratory at the direction of the Sponsor.

10.3.2 Treatment after Initial Radiologic Progression

Immune related RECIST (irRECIST) (Appendix 4) will be utilized to account for the unique tumor response characteristics seen with atezolizumab treatment. Immunotherapeutic agents such as atezolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and a clinical response may manifest after an initial increase in tumor burden or even the appearance of new lesions.

Patients with a first radiological evidence of progressive disease, should continue on study treatment, at the discretion of the investigator, until confirmed progressive disease is determined per irRECIST in a subsequent scan. Therefore, the following process for assessing radiological progressive disease will be used in this study:

1. If radiologic imaging demonstrates initial evidence for PD, tumor assessment should be repeated at the earliest of 4 weeks, or preferably on the study schedule of 6 weeks, in order to confirm PD. Treatment on-study may be continued while awaiting radiologic confirmation of progression. This clinical decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data.
2. Specifically, it is recommended that patients continue to receive study drug while waiting for confirmation of PD if they are clinically stable as defined by:
    - Absence of signs and symptoms indicating PD.
    - No decline in ECOG performance status.
    - Absence of rapid PD.
    - Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

As per irRECIST, if repeat imaging does not show irPD, then PD by irRECIST will not have been confirmed and treatment may be continued. If repeat imaging confirms irPD, PD will have been confirmed and the patient will be discontinued from study treatment.

Table 10-2 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at next scheduled time point to confirm PD	May continue study drug at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at next scheduled time point to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms irPD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR or CR (per irRECIST)	Continue regularly scheduled imaging assessments	Continue study drug at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study drug if condition has improved and/or clinically stable per Investigator's discretion

NOTE: If a subject has confirmed radiographic progression (i.e. 2 scans at least 4 weeks apart demonstrating progressive disease), but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Medical Monitor. In this case, if treatment is continued, tumor imaging should continue to be performed following the study required intervals per Table 1-1.

When feasible, patients should not be discontinued until PD is confirmed. However, patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD and should come off study treatment.

10.4 Protein Lysine Acetylation and Immune Correlates

Based on preclinical studies it is suggested that entinostat may specifically target a population of MDSCs and thus improve the response to PD1 or PDL1 antibody treatment. The Sponsor plans to evaluate populations of MDSC and other myeloid cells in peripheral blood and tumor tissues of the patients (if available) and also to evaluate the basic T-cell function in patients, with the expectation that if MDSC level is decreased the response to antigens would be improved.

10.4.1 Blood

Thirty (30) mL of blood for immune correlates is to be collected pre-dose on C1D1, C2D1, C2D15, C3D1 and at EOT for analysis at the Wistar Institute. Five (5) mL of blood will be collected pre-dose on C1D1, C2D1, C2D15 and at EOT for immune correlate analysis at

Serametrix Laboratory. Blood is to be collected and prepared according to the instructions provided in the Laboratory Study Manual.

Sixteen (16) mL of blood for protein lysine acetylation is to be collected pre-dose on C1D1 and C1D15, for analysis at the National Cancer Institute in the United States.

The following are immune correlate analyses that may be performed on the collected samples:

- MDSCs, PNM-MDSCs, Monocytes, DCs, Neutrophils, B cells
- Protein lysine acetylation in PBMCs
- Peripheral T-cell activation and Treg panels, Proliferation (Ki-67)
- Functional/proliferation assay with PBMCs using CD3/CD28, ConA and tetanus toxoid
- Plasma analysis for chemokine/cytokines (IL18, CXCL10, CXCL9, IL6, CRP)
- Antibody to tumor Antigen using peptide array
- Whole exome sequencing for Germline identification

Refer to the Study Laboratory Manuals for Covance and Serametix for instructions on sample collection and shipment.

10.4.2 Tumor Tissue

Fresh tumor tissue core biopsy samples will be collected during the study as follows:

- During **screening** from **all** patients on a **mandatory** basis.
- On **C2D15 (+/-3 days)** on an **optional** basis from patients in **the Dose Determination Phase**. Patients will be encouraged to provide an optional biopsy in order to help understand dose-immune correlate effects.
- On **C2D15 (+/-3 days)** on a **mandatory** basis until 20 samples are obtained in the Phase 2 portion of the study and on an **optional** basis for subsequent patients in this Phase 2 Expansion.
- At the time of progressive disease on an optional basis for all patients
- At the end of study treatment prior to the start of another systemic therapy, on an **optional** basis for all patients

Note: Archival tissue should also be collected at time of screening when available.

If, based on an interim review of tumor tissue data from the initial patients in Phase 2, such data are considered informative, then tumor tissue samples will be collected on a mandatory basis from all subsequent patients in the study. Alternatively, if such data are not considered informative, these samples will not be collected from subsequent patients.

Tissue samples will be sent to a central laboratory facility for preparation and distribution to other central laboratories for analysis. In addition to protein lysine acetylation testing, pre and post treatment tissue samples will also be analyzed for the following:

- PD-L1 expression level
- MDSCs – CD33+, S100A9+
- Macrophage – CD163+ or CD68+
- Neutrophil – Neutrophil elastase+
- CD8/Ki-76
- Dendritic cells – DC-SIGN (CD209)
- MHC class I
- FoxP3, CD4, CD8, granzyme B positive cells
- Gene expression – nanostring
- Whole exome sequencing and RNAseq

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

10.5 Pharmacokinetics

10.5.1 Entinostat

Blood samples for determination of entinostat levels will be collected at the following time points:

- Pre-dose C1D1
- 2-4 hours post dose C1D1 (1 sample)
- C1D8 (1 sample, anytime post dose)
- C1D15 (1 sample, anytime post dose)
- Pre-dose C2D1

On each sample collection day, the time and date of entinostat administration, the start and stop time of atezolizumab administration, and the time and date of PK sample collection should be recorded in the eCRF.

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

10.5.2 Atezolizumab

Blood samples for determination of atezolizumab levels and anti-atezolizumab antibodies will be collected at the following time points:

- Pre-dose on C1D1
- C1D1 30 minutes (+/- 10 minutes) post infusion (for atezolizumab level only)
- Pre-dose on C2D1
- Pre-dose on C4D1.
- End of Treatment
- Day 120 after coming off study treatment if patient is still being followed as per the protocol.

On each sample collection day, the time and date of entinostat administration, the start and stop time of atezolizumab administration, and the time and date of sample collection should be recorded in the eCRF.

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

10.6 TRegs and Ki67

Six (6) mL of blood will be collected from all study patients in the United States for analysis of T regulatory cells and cell proliferation pre-dose on C1D1, C2D1, C3D1 and EOT.

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

10.7 Atezolizumab Plasma Biomarker

Six (6) mL of blood will be collected from all study patients for analysis of plasma biomarkers pre-dose on C1D1, C2D1, C2D15, C3D1 and EOT.

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

10.8 Atezolizumab Serum Biomarker

Three and one-half (3.5) mL of blood will be collected from all study patients for the analysis of serum biomarkers pre-dose on C1D1, C2D1, C2D15, C3D1 and EOT.

Refer to the Study Laboratory Manual for instructions on sample collection and shipment.

11.DISCONTINUATION AND REPLACEMENT OF PATIENTS

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to, or is unable to, continue further study participation. Withdrawal of partial consent means that the patient does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures or follow-up contact). Any patient may withdraw full or partial consent to participate in the study at any time during the study. The level of study withdrawal is to be noted in the source documentation.

In the event of discontinuation of all treatment or full withdrawal from the study, the Investigator will complete the End of Study form and indicate the date and the appropriate reason. To the greatest extent possible, the Investigator will attempt to complete protocol-required follow-up tests.

During the Phase 1b Dose Determination Phase, patients who discontinue the study for reasons other than study drug-related toxicity before completing C1 may be replaced.

Reasons for permanently discontinuing study therapy and/or observation might include:

- ineligibility
- withdrawal of consent
- administrative decision by the Investigator or Syndax
- pregnancy
- significant protocol deviation or patient noncompliance
- unacceptable toxicity
- confirmed progressive disease
- the investigator believes it is no longer in the patient’s best interest to continue study therapy

During the Phase 2, the number of patients may be increased by 6-10 additional patients to accommodate for a higher than expected number of drop outs without PFS.

12. ADVERSE EVENTS, DATA REPORTING, AND RECORDING

12.1 Study Drugs

12.1.1 Entinostat

Commonly encountered AEs across clinical studies of entinostat monotherapy in patients with solid tumors included hypoalbuminemia, fatigue, nausea, hypophosphatemia, anemia, and thrombocytopenia. Incidence and severity were dose- and schedule-dependent. In a Phase 2, randomized, placebo-controlled study in patients with breast cancer, in which patients received exemestane+entinostat or exemestane+placebo, treatment-emergent adverse events (TEAEs) occurring at a ≥10% higher incidence in entinostat-treated patients versus placebo-treated patients included fatigue (48% vs 26%), nausea (40% vs 15%), neutropenia (30% vs 0%), peripheral edema and vomiting (both 21% vs 5%), thrombocytopenia (19% vs 6%), pain (16% vs 6%), and dyspepsia and leukopenia (both 14% vs 3%). The only Grade 3 or 4 AE occurring at a >10% incidence for entinostat vs placebo was neutropenia (14% vs 0%). In a Phase 2 study in patients with metastatic melanoma treated with entinostat monotherapy, the most common TEAEs were nausea (39%), hypophosphatemia (29%), pain in extremity (21%), and back pain and diarrhea (each 18%) (Hauschild 2008).

Additional clinical experience is summarized in the entinostat IB. As stated previously, there are no clinical data with entinostat in combination with atezolizumab.

12.1.2 Atezolizumab

Please refer to the current Informed Consent and the Investigator's Brochure for the current safety profile and information regarding atezolizumab.

12.2 Adverse Event Definitions

12.2.1 Adverse Events

An AE is defined in the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (ICH E6:1.2).

Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

PD should not be recorded as an AE. If PD occurs, record the date first documented in the EOT visit eCRF. Also record all methods of assessment, i.e., 1 target/non-target lesion, tumor response assessment, and/or clinical disease assessment. Indicate if the patient starts new treatment.

In the case of death, record “Fatal” for only the event causing death. AEs that are ongoing at the end of the study or time of death are to be noted as “not recovered/not resolved.” Classification of AEs is to be done by the Investigator in accordance with the NCI CTCAE, version 4.03. The Death eCRF must also be completed.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual patient represents a significant change from baseline. In general, abnormal laboratory findings without clinical significance (based on the Investigator’s judgment) should not be recorded as AEs; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered AEs.

12.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of regulatory safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

12.2.3 Unexpected Adverse Event

An unexpected AE or suspected adverse reaction is considered “unexpected” if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information

described in the General Investigational Plan or elsewhere in the current application, as amended.

12.2.4 Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- is fatal
- is life-threatening (i.e., places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a significant medical hazard, such as new malignancy

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a health care facility. Any AE that does not meet one of the definitions of serious (i.e., emergency room visit, out-patient surgery, or requires urgent investigation) may be considered by the Investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event (SAE).

12.3 Reporting Procedures for All Adverse Events

The Investigator is responsible for ensuring that all AEs (as defined in Section 12.2) observed by the Investigator or reported by patients are properly captured in the patients' medical records and reported in the Adverse Event eCRF.

The following AE attributes must be assigned by the Investigator: event description (with detail appropriate to the event); seriousness; dates of onset and resolution; severity; assessment of relatedness to entinostat and to atezolizumab; and the action taken. The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records.

If applicable, the study drug relationship will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the combination of entinostat

with atezolizumab?" The causal relation between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- **Related**: event can be fully explained by administration of the study drugs
- **Possibly related**: event may be explained by administration of the study drugs, or by the patient's clinical state or other agents/therapies
- **Unlikely related**: event is most likely to be explained by the patient's clinical state or other agents/therapies
- **Not related**: event can be fully explained by the patient's clinical state or other agents/therapies

When assessing the relationship between administration of the study drug and the AE, the following should be considered: follows a temporal sequence from administration of investigational product is a known response to the investigational product based on clinical or preclinical data could not be explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapy administered to the patient disappears or decreases upon cessation or reduction of dose of investigational product reappears or worsens when investigational product is reinstated.

Whenever possible, the CTCAE, version 4.03, should be used for assessing the severity of AEs (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

For AEs that are not adequately addressed in the NCI CTCAE, the standard severity grading scale may be used (Table 12-1).

Table 12-1 Standard Severity Grading Scale

Grade	Standard Adverse Event Severity Scoring System	
1	Mild:	Aware of sign or symptom, but easily tolerated.
2	Moderate:	Discomfort enough to cause interference with usual activity.
3	Severe:	Incapacitating with inability to work or do usual activity.
4	Life-Threatening:	Refers to an event in which the patient was, in the view of the Investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5	Fatal:	Event resulted in death.

It will be left to the Investigator's clinical judgment to determine whether an AE is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable AE. If either of these situations arises, the patient should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

12.4 Serious Adverse Event Reporting Procedures

SAEs will be collected and recorded throughout the study period, beginning with the signing of the informed consent form through 90 days after the last dose of study drug, or after the end of the study if thought to be related to entinostat or the combination. All SAEs must be reported to Syndax or its representative within 24 hours of discovery or notification of the event. Initial SAE information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and provided to Syndax or its representative. The SAE reporting procedure is provided in the Study Manual.

For all deaths, available autopsy reports and relevant medical reports should be provided to Syndax or its representative. If a patient is permanently withdrawn from the study because of an SAE, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the EOS eCRF.

The Investigator should notify the IRB or EC of SAEs occurring at the site and other AE reports received from Syndax, in accordance with local procedures and statutes.

12.4.1 Pregnancy and Lactation Reporting Procedures

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study or within 120 days of last dose of study drugor 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (Important Medical Events). Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Study Manual.

If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Please refer to the Study Manual for further details on the pregnancy reporting procedure and associated report form.

12.4.2 Definition of an Overdose and Reporting of Overdose to the Sponsor

For this study, a study drug overdose will be defined as any amount over the specified dose of 1,200 mg dose for atezolizumab and >15 mg for entinostat. No specific information is available on the treatment of overdose of Atezolizumab or entinostat. If such an event occurs, TRIO should be immediately notified and the patient observed closely for signs of toxicity. Any toxicity that occurs as a result of the overdose will be captured on the AE eCRF within 24 hours of site awareness. Appropriate supportive treatment should be provided if clinically indicated. An overdose will not be considered an SAE unless the outcome of the SAE meets seriousness criteria as defined in Section 12.2.4 Serious Adverse Events.

12.4.3 Adverse Events of Special Interest with Atezolizumab

Selected non-serious and SAEs are also known as AESI, Adverse Events of Special Interest. As noted in Section 9.6, DLTs will also be captured as AESI. AESI must be recorded as such in

the AE eCRF, completing the same fields as for Serious Adverse Events, and reported within 24 hours to the Sponsor. Such events must be documented through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier. Sponsor Contact information can be found in the Study Manual.

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 determine 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, mycophenolate, or TNF-α inhibitors.

The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

For the management of other adverse events associated with the atezolizumab not provided below, refer to the Atezolizumab IB. Patients should be assessed for possible AESIs prior to each dose of study medication. Laboratory results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an AESI thought to be immune-related should have additional testing to rule out other causes. If laboratory results or symptoms indicate a possible immune-related AESI, then additional testing should be performed to rule out other causes. If no other cause is found, then it is assumed to be immune-related.

The following conditions may be suggestive of an autoimmune disorder and are considered AESI for this study:

- Pneumonitis
- Colitis
- Endocrinopathies: Diabetes mellitus, Pancreatitis, Adrenal Insufficiency, Hyperthyroidism, and Hypophysitis
- Vasculitis

- Cases of potential drug-induced liver injury that include AST or ALT >3x ULN in combination with bilirubin >2x ULN
- Hepatitis Transaminitis: including AST/ALT >10x ULN
- Systemic Lupus Erythematosus
- Neurologic Disorders: Guillain Barre Syndrome, myasthenic syndrome or Myasthenia Gravis, and meningoencephalitis
- Grade ≥2 Cardiac Disorders (e.g., Atrial fibrillation, Myocarditis, Pericarditis)
- Events suggestive of hypersensitivity, infusion related reactions, cytokine release syndrome, influenza like illness, SIRS, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Autoimmune hemolytic anemiaSevere cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Suspected transmission of an infectious agent by the study treatment, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

12.4.4 Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be possibly related or related to study drug (as defined in section 12.3) until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

12.4.5 Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to patients. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of study drug according to IRB/EC procedures.

12.4.6 Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the Investigators, will decide whether the patient should continue to participate in the study. All protocol deviations and corresponding remediation plan will be tracked in the TRIO Clinical Trial Management System.

Period of Observation:

The table below summarizes the different periods of observation of AE, SAE, AESI with Atezolizumab and Pregnancy/Lactation.

Type of Event	AE	SAE	AESI with Atezolizumab	Pregnancy/Lactation
Reporting period	From consent until 30 days after the end of the treatment	From consent until 90 days after the last dose of study treatment for all SAEs, and any time after the end of study for SAEs believed related to entinostat or the combination	From consent until 90 days after the last dose of study treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier	From consent until 120 days after the last dose of study treatment or 30 days following the discontinuation of the study treatment in case of the start of a new anticancer therapy Note: all patients becoming pregnant must be followed up

				to the completion / termination of the pregnancy.
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Within 24 hours	Within 24 hours	Within 24 hours

12.5 Safety Monitoring

The safety and tolerability of the investigational treatments will be monitored throughout the course of the study by the Investigator and the Medical Monitor. Additionally, an independent data safety monitoring board (DSMB) will be established for the Phase 2 portion of this study to act in an advisory capacity to the Sponsor with respect to safeguarding the interests of trial patients and assessing the safety of the interventions administered during the trial.

The safety and tolerability data that will be reviewed by the Medical Monitor and DSMB will include, but are not limited to, adverse events, laboratory test results, and patient discontinuations. Additionally, the development of serious adverse events will be assessed by the Medical Monitor and DSMB on a continuous basis. Note: All serious adverse events must be reported to the Sponsor within 24 hours of discovery or notification of the event. No formal safety stopping rules are specified in the protocol. However, if any significant safety issues arise, a decision to modify or terminate the trial will be made by the Sponsor in collaboration with the DSMB and the study's Steering Committee.

13.STATISTICAL CONSIDERATIONS

13.1 Sample Size Estimation

13.1.1 Dose Determination Phase

Three to 6 patients will be enrolled in each dose cohort based on a standard Phase 1 dose-finding scheme. The total number of patients to be enrolled in the dose determination phase is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose adjustments required to achieve either the MTD or the recommended Phase 2 dose. Therefore between 6 and 18 patients will be included in the Dose Determination Phase 1 part. Note: patients who discontinued the study for reasons other than study drug related toxicities before completing cycle 1 may be replaced.

A starting sample size of 3 evaluable patients per dose cohort, expanding to 6 in the event of a marginal DLT rate (33%) was deemed to be a safe and conventional approach in dose-finding. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 83% chance that dose escalation would be halted in a given cohort.

13.1.2 Expansion Phase

The Expansion Phase will evaluate the efficacy and safety of entinostat when administered at the recommended Phase 2 dose with atezolizumab in a randomized, double-blind, placebo-controlled setting. Up to 70 eligible patients with metastatic TNBC will be randomized to receive atezolizumab with entinostat or placebo in a 1:1 allocation.

The true median PFS for patients with aTNBC receiving atezolizumab monotherapy is expected to be approximately 4 months from the initiation of such treatment. It is hypothesized that the combination of entinostat and atezolizumab will improve true median PFS by 3 months (i.e., from 4 to 7 months). Under the exponential distribution, such an improvement in median PFS represents a reduction of 43% for the true PFS failure hazard rate or equivalently, a hazard ratio of 0.57. Inferential comparisons will be performed using a stratified log-rank test, stratifying on the randomization stratification factor of geographic location. Total information of 60 PFS failures, defined as documented progressive disease by RECIST 1.1 or death due to any cause

without documented progressive disease beforehand, is estimated to provide 80% power to detect a 43% reduction in the PFS failure hazard rate with 1-sided significance level of 0.1 (SEQDESIGN procedure, SAS version 9.2).

Assuming approximately 9 months of accrual and an additional 9 months of follow-up, total accrual of 70 patients (approximately 35 per treatment arm) is projected to result in 60 PFS failures within approximately 18 months of the first patient randomization. Patients who discontinue study treatment for reasons not due to documented progressive disease by RECIST 1.1 will continue to undergo disease assessments until the earlier of documented progressive disease, death, or withdrawal of consent/lost to follow-up. It is anticipated that the number of patients who will drop out of the study without PFS failure beforehand will be low (2–3%). Depending on the actual number of such dropouts, the number of patients accrued may be increased by 6–10 additional patients to accommodate for a higher-than-expected number of dropouts.

13.2 Phase 2 Interim Efficacy Analyses

The sample size and number of PFS failures were adjusted using the O'Brien

-Fleming group sequential procedure to account for 1 planned interim analysis of PFS after 45 events (75% information). It is projected that 75% and 100% of total information will be reported at approximately 12 and 18 months, respectively.

The interim analysis will be performed to support the Sponsor's product development plans and ongoing resourcing activities. Although there are no plans to terminate the study early because of early evidence of superior efficacy for the combination treatment, the significance levels at the interim analysis and final analysis will be adjusted to maintain control of the overall type I error rate for multiple testing of PFS (O'Brien 1979).

13.3 Populations for Analysis

The Full Analysis Set (FAS) will serve as the primary population for the analysis of PFS and other efficacy-related endpoints in the Phase 2 portion of the study. The FAS will include all patients who undergo randomization, irrespective of the actual receipt of study treatment. Patients will be grouped for analysis according to the treatment arm to which they were randomized.

The Per-protocol Analysis Set is for various supportive analyses that may be performed; this excludes patients with important deviations that may substantially affect the results of the primary efficacy analyses. The final determination on protocol violations, and thereby the composition of the per-protocol set, will be made prior to locking the clinical database will be documented in a separate memo.

The Safety Analysis Set will be used for the analysis of safety data in both the Phase 1b and Phase 2 portions of the study. The safety population will consist of all patients who receive at least 1 dose of either entinostat or atezolizumab. At least 1 laboratory or other safety-related assessment subsequent to at least 1 dose of entinostat and atezolizumab is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

A patient that experiences an AE meeting DLT criteria during Cycle 1 or who receives the full dose of atezolizumab and all doses of entinostat during Cycle 1 without experiencing a DLT, is considered a DLT-evaluable patient.

13.4 Study Endpoints

The primary endpoint of the Phase 1b Dose Determination portion of the study is the recommended Phase 2 dose as assessed by incidence of DLT and overall tolerance.

The endpoints of the randomized Phase 2 Expansion portion of the study are as follows:

Primary Efficacy

- PFS, as determined by the local investigator using RECIST 1.1

Secondary Efficacy

- PFS as determined by irRECIST
- ORR (CR or PR), by RECIST 1.1 and irRECIST

- CBR (CR, PR, or SD for at least 24 weeks)
- OS
- TTR and DOR (in patients who experience a best overall response of CR or PR)

Safety

- AEs, clinical laboratory parameters, vital signs, physical exams

Exploratory:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.5 Statistical Methods

13.5.1 General

The statistical analyses performed for this study will be presented by study phase. For the Dose Determination phase, tabulations will be provided by dose cohort and overall. For the expansion phase, tabulations will be provided by treatment arm. Some analyses may be performed based on both phases combined.

The statistical analyses will be performed using SAS® version 9.2 or later (SAS Institute Inc, Cary NC). Programming specifications will be prepared which describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of CDISC's Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM). The

source SDTM and ADaM datasets from which a statistical analysis is performed (including interim reviews) will be archived with the Sponsor.

13.5.2 Patient Disposition

The number of patients included in each analysis set will be summarized, along with the reason for any exclusions. Patients discontinuing from study treatment and/or withdrawing from study participation the primary reason for discontinuation will be summarized.

13.5.3 Demographics and Characteristics

Descriptive summaries of demographic and screening characteristics will be tabulated for each study phase.

13.5.4 Extent of Exposure

The overall duration of study treatment administration and number of cycles initiated will be tabulated for each patient and summarized for each study phase. For each patient, the cumulative doses administered (in mg) of both entinostat and atezolizumab will be calculated. These data will be further summarized for each dose cohort (or treatment arm) by calculating the mean, standard deviation, median, and range of these values. The number and proportion of patients with one or more dose modifications (i.e., reduction or delay) will be tabulated along with the reason for modification.

13.5.5 Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set. With the exception of PFS, all hypothesis testing will be assessed using a one-sided significance level of 0.1. The Lan-DeMets alpha spending function with an O'Brien-Fleming type boundary will be used to control the overall type I error for multiple testing of PFS. The boundary will be derived based on the actual number of PFS failures reported for each analysis.

The primary efficacy endpoint is duration of PFS, defined as the number of months from randomization to the earlier of progressive disease or death due to any cause. Disease assessments will continue until progressive disease, even after the originally assigned study treatment is discontinued. For purposes of analysis, one month is considered 30.4375 days.

The duration of PFS will be summarized descriptively using the Kaplan-Meier method with 95% confidence intervals calculated using Greenwood's formula. Inferential comparisons between treatment arms will be made using the stratified log rank test, stratifying on the randomization stratification factor of geographic location. Estimation of the hazard ratio for treatment effect and its corresponding 95% confidence interval will be determined using a stratified Cox proportional hazards model, without any other covariate. Homogeneity in the hazard ratios between randomization strata will be examined by Wald's test. The corresponding results without stratification will be reported as supplemental analyses. The adequacy of the Cox model will be evaluated, including an assessment of the proportional hazards assumption (Therneau 2000).

For the interim and primary analyses, PFS will be right-censored for patients who meet one or more of the following conditions:

- Patients with no screening or post-screening disease assessments unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event)
- Patients who initiate subsequent anticancer therapy in the absence of documented progression
- Patients who die or have progressive disease after missing 2 or more consecutively scheduled disease assessment visits
- Patients who are last known to be alive and progression-free on or before the data cut-off date

For such patients, the progression or censoring date will be determined based on described conventions (FDA 2007). Sensitivity analyses will be performed to assess the impact of the different censoring mechanisms and deviations from the planned schedule of disease assessments (Bhattacharya 2009; Stone 2011).

ORR will be estimated based on the crude proportion of patients in each treatment arm whose best overall response during the course of study treatment is CR or PR. Tumor response will be assessed using irRECIST. Approximate 95% confidence intervals will be calculated by treatment arm for the true ORR. The inferential comparison of the observed ORRs will be made using the Cochran-Mantel-Haenszel chi-square test, stratified by the randomization stratification factors. The corresponding results without stratification will be reported as supplemental analyses.

DOR will be calculated for patients who achieve CR or PR. For such patients, DOR is defined as the number of months from the start date of PR or CR (whichever response occurs first) and subsequently confirmed, to the first date that recurrent or progressive disease is documented. The date of progression or censoring for DOR will be determined using the conventions described for PFS. DOR will be summarized descriptively for each treatment arm using the Kaplan-Meier method. Inferential comparisons between treatment arms for DOR are not planned.

CBR will be estimated based on the crude proportion of patients in each treatment arm whose best overall response during the course of study treatment is CR, PR, or stable disease lasting for at least 24 weeks. Stable disease will be measured from the start date of study treatment until the criteria for progressive disease is first met. The analysis of CBR and its duration will be based on the methods described above for ORR and DOR, respectively.

OS is defined as the number of months from randomization to the date of death (due to any cause). Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact or data analysis cutoff date, whichever date occurs first. The analysis of OS will be based on the methods described above for PFS.

13.5.6 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, vital signs, physical exam and ECG results. Unless specified otherwise, the safety analyses will be conducted for the safety population. An interim safety analysis is planned following the completion of Cycle 1 for the first 20 patients enrolled in the Phase 2 expansion phase and will utilize a Data Safety Monitoring Board.

Summary tables and listings will be provided for all reported Treatment Emergent Adverse Events (TEAEs), defined as AEs that start on or after the first administration of study treatment. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of patients experiencing the event by MedDRA system organ class (SOC) and preferred term (PT). In the event a patient

experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study treatment will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- all TEAEs
- TEAEs by relationship to study treatment and maximum severity grade
- TEAEs with action of study treatment delayed/interrupted or dose reduced
- TEAEs with action of study treatment discontinued
- SAEs

For the escalation phase, the observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experienced DLT with a 2-sided 95% exact binomial CI.

All deaths that occur on study (defined as during treatment or within 30 days of treatment discontinuation) will be reported in a patient listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range as follows:

- baseline value
- minimum post baseline value
- maximum post baseline value
- average post baseline value
- last post baseline value

Laboratory values will be assigned toxicity grades when available using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values.

ECG results will be listed and summarized in terms of the number and percentage of patients with abnormal and normal findings, as reported by the Investigator, at the time points assessed (screening and EOT).

Prior and concomitant medications will be coded to generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated and listed by patient.

13.5.7 Pharmacokinetic and Antidrug Antibody Analyses

A population PK analysis will be used to describe the PK of entinostat. The effects of patient factors (e.g., demographics, clinical chemistries, disease) on entinostat PK will be evaluated. In addition, the relationship between entinostat exposure parameters and indicators of safety will be assessed.

Specific details for these analyses as well as analyses of trough atezolizumab levels and anti-atezolizumab antibodies will be provided in a separate analysis plan.

13.5.8 Correlative Analyses

Immune correlate values will be summarized in a descriptive manner. For immune correlates measured on a continuous scale, the number of patients with no missing data, mean, either the standard error or standard deviation, median, 25^{th} percentile (first quartile), 75^{th} percentile (third quartile), minimum, and maximum values will be presented. For discrete data, the frequency and percent distribution will be presented. The Wilcoxon signed rank test (for within-treatment comparisons) and Wilcoxon rank sum test (for between-treatment comparisons) will be used to identify any systematic changes in biomarker levels from baseline. Additionally, the correlation among the various initial immune correlate values may be assessed by calculating Spearman's correlation coefficient. Analysis of covariance models may be used to explore the relationship between changes in immune correlates and selected measures of antineoplastic activity (e.g., maximum change from baseline in the sum of product diameters in measurable lesions). The association among the various immune correlates and clinical outcomes (data permitting) may be explored using heat map and other data visualization techniques.

14.REGULATORY OBLIGATIONS

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directives 2001/20/EC and 2005/28/EC and the US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

14.1 Informed Consent

A template informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from Syndax or designee to the Investigator.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures are conducted or any investigational products are administered. The acquisition of informed consent should be documented in the patient's medical records, and the informed consent form should be countersigned by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

14.2 Institutional Review Board (IRB)/Ethics Committee (EC)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/EC for written approval. A copy of the written approval of the protocol and informed consent form, in addition to other essential regulatory documents per Section 14.3, must be received by Syndax or designee before recruitment of patients into the study and shipment of study drug.

The Investigator must submit and obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IRB/EC of deviations from the protocol or SAEs occurring at the site and other AE reports received from Syndax, in accordance with local procedures.

When required, the Investigator will be responsible for obtaining annual IRB/EC renewals throughout the duration of the study. Copies of the Investigator's submission and the IRB/EC continuance of approval must be sent to Syndax or its representative.

14.3 Pre-study Documentation Requirements

The Investigator is responsible for providing the following documents to Syndax or its representative before study initiation can occur:

- Signed and dated protocol signature page (Investigator's Agreement).
- Completed Food and Drug Administration form 1572 or equivalent per local regulatory requirements.
- Curricula vitae of Principal Investigator and all sub-investigators (updated within 12 months).
- Copy of the IRB/EC approval of the protocol, consent form, and patient information sheet.
- IRB/EC composition or written statement that the board is in compliance with regulations.
- Laboratory normal ranges and documentation of laboratory certification (or equivalent).
- Signed Clinical Trial Agreement between Syndax or its representative and the authorized representative at the institution, or investigator if applicable.
- Completed Financial Disclosure statements for the Principal Investigator and all sub-investigators.

14.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. In the eCRFs or other study documentation submitted to Syndax or its representative, patients should be identified only by their initials (unless prohibited by local regulatory guidelines) and a patient ID number. Patient samples should be identified only by the patient ID number. Documents that are not for submission to Syndax or its representative (i.e., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with federal guidelines and applicable local regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

15.ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Protocol Amendments and Study Termination

All protocol amendments will be implemented by Syndax and must receive Health Authority (where required) and IRB/EC approval before implementation, except where necessary to eliminate an immediate hazard to patients. The Investigator **must** send a copy of the approval letter from the IRB/EC, along with the revised Informed Consent form, to Syndax or its representative.

Both Syndax and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to Syndax or its representative.

15.2 Study Documentation and Archive

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Syndax Delegation of Responsibility Form.

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of study-related documentation, available for inspection and audit at any time by representatives from Syndax and/or applicable regulatory authorities. Elements should include:

- Patient files containing informed consent forms and patient identification list.
- Study files containing the Protocol with all amendments, Investigator's Brochure, copies of pre-study documentation (Section14.3), and all correspondence to and from the IRB/EC and Syndax.
- Investigational Product Accountability Records and all drug-related correspondence.

In addition, all original source documents supporting entries on the eCRFs must be maintained and be readily available. Source documents should be retained by the investigator according to ICH-E6 and local regulations or as indicated in the clinical study agreement, whichever is longer.

No study document should be destroyed without prior written agreement between Syndax and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Syndax in writing of the new responsible person and/or the new location.

15.3 Study Monitoring and Data Collection

A study monitor will be responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities; verifying the eCRFs at regular intervals throughout the study to assess adherence to the protocol; ensuring completeness, accuracy, and consistency of the data; and ensuring adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In addition to routine monitoring and in accordance with United States 21 CFR Parts 312, 50, and 56, the ICH GCP and applicable local regulatory requirements, the study site may be selected for audit by a designee of Syndax or its representative and/or regulatory inspection by appropriate regulatory authorities. Inspection and audit of site facilities (i.e., pharmacy, drug storage areas, laboratories) and review of study-related records may occur to evaluate the study conduct and compliance with the protocol and applicable regulatory requirements.

Agreements between Syndax, the Institution and/or Principal Investigator regarding study payments, insurance coverages and publication policy are covered in the clinical trial agreement and not in this protocol.

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17. APPENDICES

17.1 Appendix 1 New York Heart Association (NYHA) Classification of Heart Failure

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking 1 to 2 blocks on the level and climbing more than 1 flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

17.2 Appendix 2 Concomitant Medications to be Avoided

Examples of sensitive *in vivo* CYP substrates and CYP substrates with narrow therapeutic range are summarized in Table 17-1.

Table 17-1: Examples of substrates that may be affected by entinostat

CYP Enzymes	Substrates with narrow therapeutic range[1]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP3A[2]	Alfentanil, astemizole[3], cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

[1] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes).

2 Because a number of CYP3A substrates (e.g. darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

3 Withdrawn from the United States market because of safety reasons.

Table 17-2 P-gp Inhibitors and Inducers

	Inhibitor	Inducer
P-gp, MDR1	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone,felodipine, lopinavir,quercetin, ranolazine, ticagrelor, ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine	Avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort, tipranavir/ritonavir

17.3 Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Dysautonomia	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Epidermolysis bullosa acquista	Optic neuritis
Antiphospholipid antibody syndrome	Gestational pemphigoid	Ord's thyroiditis
Aplastic anemia	Giant cell arteritis	Pemphigus
Autoimmune hemolytic anemia	Goodpasture's syndrome	Pernicious anemia
Autoimmune hepatitis	Graves' disease	Polyarteritis nodusa
Autoimmune hypoparathyroidism	Guillain-Barré syndrome	Polyarthritis
Autoimmune hypophysitis	Hashimoto's disease	Polyglandular autoimmune syndrome
Autoimmune myocarditis	IgA nephropathy	Primary biliary cirrhosis
Autoimmune oophoritis	Inflammatory bowel disease	Psoriasis
Autoimmune orchitis	Interstitial cystitis	Reiter's syndrome
Autoimmune thrombocytopenic purpura	Kawasaki's disease	Rheumatoid arthritis
Behcet's disease	Lambert-Eaton myasthenia syndrome	Sarcoidosis
Bullous pemphigold	Lupus erythematosus	Scleroderma
Chronic inflammatory demyelinating polyneuropathy	Lyme disease - chronic	Sjögren's syndrome
Chung-Strauss syndrome	Meniere's syndrome	Stiff-Person syndrome
Crohn's disease	Mooren's ulcer	Takayasu's arteritis
	Morphea	Ulcerative colitis
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
	Myasthenia gravis	Wegener's granulomatosis

17.4 Appendix 4: Immune-related Response Criteria Derived from RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics. This is particularly true for immunotherapeutic agents such as anti-CTLA-4 and anti-PD1\anti PDL1 which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects (Hoos 2010; Hodi 2008). Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as RECIST and WHO criteria are not sufficient to fully characterize patterccns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria (Hoos 2010; Nishino 2014).

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria (Hoos 2010; Nishino 2012).

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST 1.1 criteria (irRECIST; Nishino 2014). .

Lesion measurability and baseline selection of lesions:

The RECIST 1.1 definitions for measurable and non-measurable lesions apply. At baseline, all tumor lesions/lymph nodes will be categorized as measurable or non-measurable. For target lesions, a Total Measured Tumor Burden (TMTB) for all target lesions will be calculated and reported as the baseline TMTB (similarly to the Sum of Diameters in RECIST 1.1). The baseline TMTB will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

New lesions:

irRECIST do not necessarily score the appearance of new lesions as progressive disease. Also, new lesions should be categorized as measurable or non-measurable (same measurability rules as RECIST 1.1. apply).

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

All new lesions not selected as New Measurable lesions are considered New Non-measurable lesions and are followed qualitatively.

Post baseline tumor assessments:

- TMTB: At each post-baseline assessment the TMTB is defined as the sum of:
  - Longest diameters of all non-nodal target lesions
  - Longest diameters of all NEW non-nodal measurable lesions
  - Short axis of all nodal target lesions
  - Short axis of all NEW nodal measurable lesions
- Non-target lesions/New Non-measurable lesions: the RECIST 1.1 definitions for the assessment of non-target lesions apply (irCR; irNN, irPD).

Overall response at each time point:

- Immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Immune-related partial response (irPR): Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions
- Immune-related stable disease (irSD): Failure to meet criteria for irCR or irPR in the absence of irPD.
- Immune-related progressive disease (irPD): Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions.
- irNE (Not evaluable): used in exceptional cases where insufficient data exists.