A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 1b/2 Study of Avelumab With or Without Entinostat in Patients with Advanced Epithelial Ovarian Cancer Which Has Progressed or Recurred After First-line Platinum-based Chemotherapy and at Least Two Subsequent Lines of Treatment with a Safety Lead-in [SNDX-275-0603]

Syndax Protocol SNDX-275-0603

Clinical Study Sponsor: Syndax Pharmaceuticals, Inc.
35 Gatehouse Drive, Building D, Floor 3
Waltham, MA 02154

Key Sponsor Contacts: [redacted]
Telephone: [redacted]
[redacted]
Telephone: [redacted]

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Amendment: 2

Confidentiality Notice

This document contains confidential information of Syndax Pharmaceuticals, the contents of which must not be disclosed to anyone other than the study staff and members of the respective Institutional Review Board/Ethics Committee.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Syndax Pharmaceuticals.

Investigator's Agreement

I have read the attached protocol entitled **"A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 1b/2 Study of Avelumab With or Without Entinostat in Patients with Advanced Epithelial Ovarian Cancer Which Has Progressed or Recurred After First-line Platinum-based Chemotherapy and at Least Two Subsequent Lines of Treatment with a Safety Lead-in [SNDX-275-0603]"**, dated 02 February 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite E6 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.

[redacted]
Signature

[redacted]
Name of Principal Investigator

[redacted]
Date

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1. SYNOPSIS SNDX-275-0603

Study Title:	A Randomized, Placebo-controlled, Double-blind, Multicenter Phase 1b/2 Study of Avelumab With or Without Entinostat in Patients with Advanced Epithelial Ovarian Cancer Which Has Progressed or Recurred After First-line Platinum-based Chemotherapy and at Least Two Subsequent Lines of Treatment with a Safety Lead-in [SNDX-275-0603]

Phase of Clinical Development: Phase 1b/2

Indication: Epithelial ovarian cancer which has progressed or recurred after initial platinum-based chemotherapy followed by at least 2 subsequent lines of treatment for recurrent cancer.

Objectives:

Primary Objective:

Phase 1b: (Safety lead-in): To determine the dose-limiting toxicities (DLTs) and maximum-tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of entinostat (SNDX-275) given in combination with avelumab

Phase 2 (Expansion Phase): To perform an evaluation of the efficacy of entinostat in combination with avelumab at the RP2D versus avelumab plus placebo in patients with refractory or recurrent epithelial ovarian cancer, as determined by the duration of progression-free survival (PFS) based on the local investigator's assessment of progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Objectives:

Efficacy: To evaluate the efficacy of entinostat in combination with avelumab in patients with advanced epithelial ovarian cancer, 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 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 confirmed response of CR or PR:

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

Pharmacokinetics: To assess the effect of entinostat on the pharmacokinetics (PK) of avelumab

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

Exploratory Objectives:

[redacted]

[redacted]

Hypotheses:

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

Phase 2: Entinostat combined with avelumab at the dose determined in Phase 1b will result in an improved PFS compared to avelumab alone

Study Design:

This is a Phase 1b/2 study evaluating the combination of entinostat plus avelumab in patients with advanced epithelial ovarian cancer. The study comprises 2 phases: an open-label Safety Lead-in (Phase 1b) followed by an Expansion Phase (Phase 2). The Expansion Phase will evaluate the efficacy and safety of entinostat with avelumab when administered at the RP2D versus avelumab alone in patients with advanced epithelial ovarian cancer in a randomized, double-blind, placebo-controlled setting. Up to 138 patients are anticipated if the study completes all phases of evaluation (up to 18 patients for Phase 1b; up to 120 patients for Phase 2). In Phase 2, patients will be randomized in a 2:1 ratio to receive avelumab plus entinostat or avelumab plus placebo, respectively. The randomization for the Phase 2 portion will be stratified by the presence of bulky disease (defined as presence of a tumor $\geq$ 50 mm) versus not and by a history of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not. Regardless of phase, patients will be screened for study eligibility within 21 days before enrollment into the study. Based on screening assessments, eligible patients will be enrolled in the study within 3 days prior to starting study treatment on Cycle 1, Day 1.

A treatment cycle is 2 weeks (14 days) in length. The dose of avelumab will be 10 mg/kg administered intravenously (IV) over 1 hour every 2 weeks (Day 1 of each cycle) for all patients. Entinostat (during the Phase 1b Safety Lead-in) and entinostat/placebo (during Phase 2, Expansion Phase) will be administered orally (PO) on Days 1 and 8 of each 14-day cycle. The Safety Lead-in will begin with a starting dose (dose level 1) of entinostat 5 mg PO weekly. If dose level 1 exceeds the MTD (i.e., if at least 2 patients experience a DLT), accrual to this dose cohort will be terminated and 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. Each dose level will be reviewed by the Sponsor Study Physician(s) in consultation with the Investigators after the majority of the safety assessments for each level are completed. The entinostat dose determined appropriate for combination with avelumab will then be taken forward into the Phase 2 Expansion Phase of the study as the RP2D.

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

- Availability of a recent formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from a de novo tumor biopsy during screening. If patients whose only accessible lesion for biopsy is a solitary target lesion, it must be amenable to a core biopsy that will not compromise assessment of tumor measurements. Alternatively, a recently obtained archival FFPE tumor tissue block (cut slides not acceptable) from a primary or metastatic tumor resection or biopsy can be provided if the biopsy or resection was performed within 1 year of randomization or if biopsy is clinically contra-indicated. Availability of an archival FFPE tumor tissue from primary tumor resection specimen (if not provided

per above). If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.

- On Cycle 4 Day 1 (+ 3 days) on an optional basis from patients in the Safety Lead-in. All patients will be encouraged to provide an optional biopsy to help understand dose-immune correlate effects.
- On Cycle 4 Day 1 (+ 3 days) on an optional basis for patients in the Phase 2 portion who consent to biopsy
- 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, tumor tissue samples may be collected on a mandatory basis from all subsequent patients on Cycle 4 Day 1 (+3 days).

Blood samples will be collected as follows:

- [redacted]
- [redacted]
- For determination of entinostat levels: pre-dose on Cycle 1 Day 1 and 2 to 4 hours post-dose; anytime post-dose on Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 4 Day 1, and pre-dose on Cycle 2 Day 8
- For determination of avelumab levels: pre-dose and at the end of infusion on Day 1 of Cycles 1 through 6, then Cycles 8, 10, 12, 16, 20, 28, 32, 36,48, EOT, and at 30-day Follow-up.
- For determination of avelumab antidrug antibody (ADA neutralizing antibodies) levels: pre-dose on Day 1 of Cycles 1 through 6, then Cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and at 30-day Follow-up.
- For serum protein signatures: pretreatment on Cycle 1 Day 1 and Cycle 4 Day 1

Patients will remain on study treatment until unequivocal progressive disease (PD), intolerable toxicity, one of the other study withdrawal criteria is met (Section 11). Patients with radiographic progression only, as defined by RECIST 1.1 should continue on study treatment until unequivocal PD is determined as defined by irRECIST (Appendix 1), at the discretion of the Investigator. After study treatment discontinuation, patients will complete an EOT visit within 7 days after the last dose of study drug and 3 Safety Follow-up visits 30, 60, and 90 days (± 7 days) after the EOT visit. The 60-day Safety Follow-up will be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care). The 90-day visit may also be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care) given that the patient's 90-day thyroid function tests are assessed locally. Patients with ongoing toxicities will be followed more frequently per the Investigator's clinical judgement and standard of care. For example, Grade 3 or higher laboratory toxicities will be assessed at least weekly until resolution to Grade 2 or baseline grade. Entinostat- and avelumab- related toxicities will be managed as outlined in Section 9.10.

After completion of the 30-day Safety Follow-up visit, patients who have not experienced PD will be followed every 6 weeks for a clinic visit and radiological imaging until unequivocal PD or until Week 36, whichever occurs first. If PD has not been documented at Week 36, patients will be followed every 8 weeks for radiological imaging until unequivocal PD, death, or end of the study, whichever occurs first. Following documentation of PD, patients 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/Safety Lead-in: Up to 18 patients are expected to be enrolled in the Dose Determination Phase of the study which employs a rolling 6 phase 1 trial design, with the determination of DLT and the MTD and/or RP2D based on entinostat in combination with avelumab in Cycle 1 and Cycle 2. Using the rolling 6 design, 2 to 6 patients can be concurrently enrolled into a dose level, dependent upon (1) the number of patients enrolled at the current dose level; (2) the number of patients who have experienced DLT at the current dose level; and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met. Six patients must be treated at a dose level before it is considered the MTD or RP2D. Patients will receive entinostat orally at the assigned dose on Days 1 and 8 along with avelumab 10 mg/kg on Day 1 of a 14-day cycle. Dose group 1 will receive 5 mg

entinostat weekly. If the entinostat 5-mg dose exceeds the MTD, then a 3-mg dose of entinostat (Dose Group -1) will be evaluated. If the entinostat 3-mg dose exceeds the MTD, then a 2-mg dose of entinostat (Dose Group -2) will be evaluated.

All patients within a cohort will complete Cycles 1 and 2, have safety assessments performed through Cycle 3 Day 1, and be assessed for DLTs 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. Six patients must be treated at a dose level before it is considered the MTD or RP2D.

If the -2 dose level exceeds the MTD, the study will be terminated 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 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 Cycle 1 and Cycle 2, 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 Phase: In the Expansion Phase, the efficacy and safety of entinostat (compared to placebo) in combination with avelumab will be evaluated using the RP2D identified in the Phase 1b/Safety Lead-in (Dose Determination) Phase. Up to 120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab plus entinostat or avelumab plus placebo in a 2:1 ratio, respectively. The randomization will be stratified by the presence of bulky disease (defined as a tumor ≥ 50 mm) versus not and by a history of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not.

An independent Data Safety Monitoring Board (DSMB) will be convened for the Phase 2 portion of the study. The DSMB will consist of clinicians and biostatisticians who are experienced in clinical trials of patients with advanced epithelial ovarian cancer and the treatments under investigation. Further details regarding DSMB membership will be described in the DSMB Charter. The primary responsibility of the DSMB is to review safety and efficacy data on a periodic basis, but not less frequently than approximately every 6 months. Unplanned safety review meetings of the DSMB may be called at any time. An initial safety evaluation will be performed based on the first 20 patients who are randomized and receive at least 1 administration of study treatment. The initial safety evaluation will be held after the first 20 patients have completed at least 4 weeks of follow-up after the initiation of study treatment or terminated therapy at an earlier time point due to toxicity. Enrollment may continue while the DSMB conducts their reviews. The assessment of the DSMB for this and subsequent safety reviews will focus on deaths (due to any cause), treatment modifications, treatment discontinuations, laboratory values, adverse events, and serious adverse events. Any adverse safety signals will be assessed by the committee based on the committee's collective clinical experience rather than on prospective statistically-based early stopping rules. Depending on the outcome of the review, the DSMB may recommend continuation, termination, or modification of the study, as appropriate.

The DSMB also will be responsible for reviewing the results of selected efficacy data once 65 PFS failures (67% of total events) occur, which is anticipated approximately 14 months after the first patient is enrolled in the expansion phase of the study. Given the early stage of development, preliminary anti-tumor activity of the investigational treatments may be evaluated by the DSMB periodically prior to the planned interim analysis to supplement the aforementioned safety reviews.

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

Number of Centers: Up to approximately 30 study centers in the US may participate.

Number/Type of Subjects: Up to 138 patients are anticipated if the study completes all phases of evaluation.
Phase 1b/Safety Lead-in: Up to 18 patients will receive entinostat plus avelumab.
Phase 2/Expansion Phase: Up to 120 patients will receive avelumab plus entinostat or avelumab plus placebo in a 2:1 ratio.

Investigational Products:

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 (HDAC) and therefore 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 is supplied in 2 strengths of film-coated tablets containing 1 mg (pink to light red) or 5 mg (yellow) of active ingredient.

Avelumab: Avelumab is a fully human immunoglobulin (Ig) G1 antibody directed against PD-L1 with a calculated molecular weight of 143,832 Dalton. The antibody is produced by mammalian cell culture in a serum-free growth medium, and is purified by affinity, ion-exchange, and mix-mode chromatography. The process also includes specific viral inactivation and removal steps. The antibody is then transferred into formulation buffer and brought to the desired concentration.

Duration of Treatment: Patients will remain on study treatment until unequivocal PD, intolerable toxicity, or one of the other study withdrawal criteria is met (Section 11).

Study Population

Inclusion Criteria:

1. Females aged 18 years or older on the day written informed consent is given
2. Histologically or cytologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer
3. Recurrent or progressive disease on or after initial platinum-based chemotherapy for the diagnosis in Inclusion Criterion #2
4. Evidence of measurable disease (according to RECIST 1.1) based on imaging studies (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) within 28 days before the first dose of study drug
5. Previously received at least 3, but no more than 6, lines of therapy including at least 1 course of platinum-based therapy
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Has adequate organ and bone marrow function within 21 days before enrollment as defined below:

System	Laboratory Value
Hematological	
Absolute neutrophil count	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine **OR**	≤ 1.5 × the upper limit of normal (ULN)
Measured or calculated[1] creatinine clearance (CrCl)[2]	≥ 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)	≤ 3.0 × ULN

[1] Creatinine clearance should be calculated per institutional standard.
[2] Glomerular filtration rate can also be used in place of creatinine or CrCl.

8. If a female of childbearing potential, has a negative urine pregnancy test during screening and a negative urine pregnancy test within 3 days prior to enrollment. If the screening pregnancy test is done within 3 days prior to enrollment, a repeat urine test is not required. A serum pregnancy test is required if the urine pregnancy test is positive. Note: Women of childbearing potential are any women between menarche and menopause (including women who have experienced menopause onset < 12 months prior to enrollment) who have not been permanently or surgically sterilized and are capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion.
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 a patient underwent major surgery or radiation therapy of >30 Gray, she 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:

1. Non-epithelial ovarian carcinomas or ovarian tumors with low malignant potential (i.e., borderline tumors)
2. Another known malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia/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.
3. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
4. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent (See Appendix 4). Patients with diabetes type I, vitiligo, psoriasis, hypo-or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
5. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry and are neurologically stable. Patients with a history of carcinomatous meningitis are not eligible.
6. 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).
7. 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:

    - 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 congestive heart disease, or a QTc interval > 470 msec;
    - Coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism within 6 months prior to screening;
    - History of Torsades de pointes, ventricular tachycardia, or ventricular fibrillation;
    - Uncontrolled hypertension or diabetes mellitus; or

- Active infection requiring systemic therapy. Uncomplicated and asymptomatic urinary tract infections are allowed with oral antibiotic treatment (intravenous antibiotics are prohibited).

8. Any contra-indication 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
9. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies)
10. 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 [HBcAb] 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.
11. Allergy to benzamide or inactive components of entinostat
12. History of allergies to any active or inactive ingredients of avelumab and known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI CTCAE v 4.03)
13. Previously treated with a histone deacetylase inhibitor (i.e., vorinostat, belinostat, romidepsin, panobinostat), PD-1/PD-L1-blocking antibody (i.e., atezolizumab, nivolumab, pembrolizumab), or a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) agent
14. Received a live vaccine within 30 days of the first dose of treatment
15. Received prior anti-cancer monoclonal antibody (mAb) or anti-vascular endothelial growth factor (VEGF) within 4 weeks prior to enrollment or has not recovered (i.e., ≤ Grade 1 at enrollment) from adverse events due to mAb agents administered more than 4 weeks earlier
16. Received prior systemic anti-cancer therapy within 4 weeks or 5 half-lives, whichever is shorter, targeted small molecule therapy or radiation therapy within 2 weeks prior to enrollment, or has not recovered (i.e., ≤ Grade 1 at enrollment) from adverse events 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.*
17. Currently receiving treatment with any other agent listed on the prohibited medication list
18. Currently enrolled in (or completed) another investigational drug study within 30 days prior to study drug administration
19. Is pregnant, breastfeeding, or expecting to conceive starting with the screening visit through 120 days after the last dose of study drug
20. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

Criteria for Evaluation

Efficacy Assessments:
During treatment, patients will attend study center visits for study evaluations on Days 1 and 8 of Cycles 1 and 2; and on Day 1 of each cycle thereafter. Patients will have radiological disease assessments performed within 28 days prior to enrollment, and then every 6 weeks (± 3 days) when measured from Cycle 1 Day 1, through Week 36 (Weeks 6, 12, 18, 24, 30, 36) until unequivocal progressive disease per RECIST 1.1. Patients remaining on study after Week 36 will undergo radiological disease assessments every 8 weeks (± 3 days) until unequivocal PD occurs. Disease will be assessed by CT and MRI as appropriate, using the same method as used for the screening evaluation, and response will be assessed by the Investigator using RECIST 1.1 and irRECIST.

Study Endpoints:

Primary Efficacy Endpoint

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

Secondary Endpoints: (analyzed for 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 or PR, or SD for at least 24 weeks) by RECIST 1.1 and irRECIST
- OS
- DOR and TTR (in patients who experience best overall response of CR or PR)
- The effect of entinostat on the PK of avelumab

Safety:

- Determination of DLT, MTD, and RP2D
- Incidence of treatment-emergent adverse events, serious adverse events, adverse events resulting in the permanent discontinuation of study drug, and deaths occurring within 30 days of the last dose of study drug
- Change from baseline in vital signs, ECOG, physical examination, electrocardiograms (ECGs), and laboratory assessments

Exploratory:

[redacted]

Statistical Methods:

Sample Size Considerations

Phase 1b/Safety Lead-in (Dose Determination Phase):

Up to 6 patients evaluable for safety will be enrolled in each dose cohort based on a Phase 1 rolling 6 design (Skolnik 2008). Each patient will be counted in only 1 dose cohort. Six patients must be treated in a dose level for it to be considered the MTD or the RP2D; therefore, the total number of patients to be enrolled in this phase will be determined by the number of necessary dose cohorts required to achieve the MTD or RP2D. Patients who discontinue for reasons other than study drug-related toxicities before competing Cycle 2 will be replaced.

Phase 2/Expansion Phase:

The Expansion Phase will evaluate the efficacy and safety of entinostat (compared to placebo) when administered at the RP2D with avelumab in a randomized, double-blind, placebo-controlled setting.

Progression-free survival will be the primary measure of efficacy; secondary measures of efficacy include ORR, CBR, DOR, TTR, and OS.

Up to 120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab with entinostat or placebo in a 2:1 allocation. The sample size was determined based on the following considerations: True median PFS for patients with advanced epithelial ovarian cancer receiving avelumab monotherapy is expected to be approximately 3 to 4 months when measured from randomization. It is hypothesized the combination of entinostat and avelumab will reduce the hazard of disease progression or death without documented disease progression beforehand by 43% (i.e., true hazard ratio of 0.57). Under the exponential distribution, such a reduction in the hazard rate represents a 75% improvement in true median PFS relative to that of the control arm. If true median PFS is 3 months for patients receiving avelumab monotherapy, then true median PFS will be improved by approximately 2.25 months (i.e., 3 vs 5.25 months). Similarly, if true median PFS is 4 months for the control arm, then true median PFS will be improved by 3.0 months (i.e., 4 vs 7 months). Total information of 97 PFS failures, defined as documented progressive disease by RECIST 1.1 or death due to any cause without prior documented PD is estimated to provide 90% power to detect the aforementioned 43% reduction in the PFS failure hazard rate with one-sided significance level of 0.10. The primary analysis of PFS will be performed using a stratified log-rank test, stratifying on the randomization stratification factor(s).

Assuming true median PFS is 4 months for the control arm and approximately 12 months of accrual plus an additional 12 months of follow-up, total accrual of 120 patients (80 in the entinostat arm and 40 in the placebo arm) is projected to result in 97 PFS failures within approximately 24 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% to 3%). Depending on the actual number of such dropouts, the number of patients accrued may be increased by 6 to 12 additional patients to accommodate for a higher-than-expected number of dropouts.

Statistical Considerations

The safety and efficacy analyses will be presented by study phase. For the Phase 1b/Safety Lead-in (Dose Determination Phase), tabulations will be provided by dose cohort and overall. Some analyses may be performed based on the Phase 1b and Phase 2/Expansion Phases combined.

Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set. Progression-free survival is the primary endpoint for the Expansion Phase and is defined in the conventional manner as the number of months from the randomization date to the earlier of documented PD or death due to any cause. Progressive disease will be assessed by the local investigator using RECIST 1.1 (primary assessment method) and irRECIST (secondary assessment method). For both assessment methods, the disease progression date and censoring date will be based on published conventions (US Food and Drug Administration 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. Progression-free survival 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(s). 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.

An interim efficacy analysis is planned after 65 PFS failures (67% of total events), which is anticipated to occur approximately 14 months after the first patient is enrolled in the expansion phase of the study. The calendar date of the 65th event will serve as the data cutoff date for the interim analysis.

The primary analysis of PFS will be based on the first 97 PFS failures, which is anticipated to occur approximately 24 months after the first patient is enrolled in the expansion phase. The calendar date of the 97th event will serve as the data cutoff date for the primary analysis. The primary analysis of the secondary and exploratory endpoints and safety will occur at the time of the primary PFS analysis. The significance levels at the interim analysis and primary analysis will be adjusted using the O'Brien-Fleming procedure to maintain control of the overall type I error rate for multiple testing.

Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set. Treatment-emergent adverse events reported during the study will be tabulated and listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Tables will display number and percentage of patients experiencing the event for the following categories: all adverse events; adverse events considered related to study treatment; adverse events by severity; DLTs; adverse events leading to treatment delay, reduction, or discontinuation; and serious adverse events. For the Phase 1b component, 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.

Hematology and serum chemistry results will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: enrollment value, minimum and maximum post-baseline values, average post-baseline value, and last post enrollment value. Standard shift tables will present worst post-baseline toxicity grade versus baseline. Vital signs will be summarized descriptively (mean, standard deviation, median, and range) in the same manner as for laboratory values.

The statistical methods to be used for the analysis and reporting of the secondary efficacy endpoints are described in Section 13.

Date of Original Approved Protocol:

19 July 2016

Table 1-1. Schedule of Study Assessments

Procedure[23]	Screening (D -21 to -1)	Combination Therapy						EOT (≤7 days of last dose)	Safety Follow-up (30 days after EOT)	Post-Study Follow-up (60 days after EOT)[1,2]	Post-Study Follow-up (90 days after EOT) [1,2]
		Cycle 1		Cycle 2		Cycle 3 and beyond	Cycle 4				
		Day 1	Day 8	Day 1	Day 8	Day 1	Day 1				
Visit Window	---	---	±1 day	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	±7 days	±7 days
Provision of written informed consent	X										
Demographics	X										
Medical and disease history	X	X									
Assess adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X[3]	X[3]						X	X		
Symptom-directed physical examination		X	X	X	X	X	X				
Electrocardiogram	X							X[4]			
Vital signs, weight (height at screening only)	X	X		X		X	X	X	X		
ECOG performance status	X	X		X		X	X	X	X		
Radiological imaging, disease assessment	X[5]						X[6]	X[7]			X[1]
Pregnancy testing	X[9]	X									
Hematology[10], coagulation studies[10], clinical chemistries[11, 12]	X	X[12]	X	X	X	X	X	X			
ACTH (baseline only) and thyroid function tests[13]	X						X[13]	X	X		X
HBV DNA, HCV RNA[14]	X[14]										

Table 1-1. Schedule of Study Assessments

Procedure[23]	Screening (D -21 to -1)	Combination Therapy						EOT (≤7 days of last dose)	Safety Follow-up (30 days after EOT)	Post-Study Follow-up (60 days after EOT)[1,2]	Post-Study Follow-up (90 days after EOT) [1,2]
		Cycle 1		Cycle 2		Cycle 3 and beyond	Cycle 4				
		Day 1	Day 8	Day 1	Day 8	Day 1	Day 1				
Visit Window	---	---	±1 day	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	±7 days	±7 days
[redacted]											
Blood sample for protein signature[17]		X					X				
Tumor tissue core biopsy sample (also archival tissue when available)	X[18]						X[18]	X[18]			
Entinostat self-administration		Self-administration on Days 1 and 8 of each cycle									
Avelumab administration[19]		X		X		X	X				
Blood sample for entinostat PK[20]		X[20]	X[20]	X[20]	X[20]	X[20]					
Blood sample for avelumab PK[21]		X[21]		X[21]		X[21]	X[21]	X[21]	X[21]		
Blood sample for avelumab ADA[22]		X[22]		X[22]		X[22]	X[22]	X[22]	X[22]		
Study drug compliance assessment		X	X	X	X	X	X	X			

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibodies; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IV = intravenously; PD = progressive disease; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell; T4 = thyroxine; TSH = thyroid stimulating hormone

Footnotes begin on the following page.

Table 1-2. Schedule of Study Assessments

Footnotes:

[1] After the Safety Follow-up visit, patients who have not experienced PD will be followed (including radiological assessments) every 6 weeks through Week 36, then every 8 weeks thereafter until PD. Thereafter, they are contacted every 3 months until death or study closure for survival status, PD, and alternate treatments.

[2] The 60-day Post-Study Follow-up visit will be conducted via telephone, unless a visit is clinically indicated due to ongoing toxicity. The 90-day Post-Study Follow-up visit may be conducted via telephone, given that thyroid function tests are still assessed for this visit. Patient must come into clinic if a visit is clinically indicated due to ongoing toxicity.

[3] If the screening complete physical examination was performed within 7 days before C1D1, a symptom-directed examination may be performed at enrollment. The complete physical examination will consist of minimum evaluation of HEENT (head, eyes, ears, nose and throat), dermatological, respiratory, cardiovascular, gastrointestinal, neurological and lymphatic, and musculoskeletal systems.

[4] An ECG is to be performed at screening; pre-dose on C7D1, every 6 cycles (12 weeks) thereafter and at EOT. An ECG may be repeated anytime, as clinically indicated.

[5] Performed only if last scan was performed > 28 days before enrollment.

[6] Patients will have radiological disease assessments performed every 6 weeks (± 3 days) through week 36 (Week 6, 12, 18, etc.) and then every 8 weeks (± 3 days) until unequivocal progression in both Phase 1b and Phase 2. Partial or complete responses 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, to confirm PD. Contrast-enhanced CT scans of chest, abdomen, and pelvis, are preferred for evaluation of disease status; 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.

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

[8] Sample collected every3 cycles (6 weeks ± 3 days) through Cycle 18 (Week 36) and then every 4 cycles (8 weeks ±3 days).

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

[10] Analytes tested: RBC, WBC with absolute counts of individual cell types, platelet count, hemoglobin and hematocrit. Screening only also includes: PT or INR and aPTT (more frequent collection required if patient is on anti-coagulant therapy per standard of care).

[11] Analytes tested: ALT, AST, albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, sodium, potassium, chloride, bicarbonate, glucose, phosphorus, and total protein. Magnesium at enrollment only, unless clinically indicated.

[12] Performed only if screening laboratory tests performed >7 days prior to enrollment.

[13] ACTH will be measured at screening only (thereafter for new toxicities only); free T4, and TSH will be measured at screening, every 8 weeks for 2 additional measurements, every 12 weeks thereafter while on treatment, at EOT, at the 30-day and 90-day Safety Follow-up visits and as clinically indicated.

[14] HBV DNA test must be performed in patients with past HBV infection or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) prior to randomization. Polymerase chain reaction is required and must be negative for HCV RNA in patients positive for HCV antibody.

[15] Samples collected pre-dose on C1D1, C2D8, C4D1, and at the End-of-Treatment visit.

[16] Sample collected before any study drug administration.

[17] Blood samples to be collected pretreatment on C1D1 and C4D1.

[18] Availability of a recent formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from a de novo tumor biopsy during screening (biopsied tumor lesion should not be a RECIST target lesion). Alternatively, a recently obtained archival FFPE tumor tissue block (cut slides not acceptable) from a primary or metastatic tumor resection or biopsy can be provided if the biopsy or resection was performed within 1 year of randomization or if biopsy is clinically contra-indicated. Availability of an archival FFPE tumor tissue from primary tumor resection specimen (if not provided per above). If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.

[19] Avelumab will be administered as an IV infusion over 1 hour. The mandatory 2-hour observation period after each avelumab infusion (for potential infusion-related reactions) is only required following the first 4 avelumab infusions. Patients who experience an infusion-related reaction at any point must continue to undergo the mandatory observation after each infusion.

[20] Samples for entinostat PK are taken pre-dose on C1D1 and 2 to 4 hours post-dose; anytime post-dose on C1D8, C2D1, and C4D1, and pre-dose on C2D8.

[21] Samples for avelumab PK will be taken pre-dose and post-infusion (PK only); Day 1 of Cycles 1 thru 6, then cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and 30-day Safety Follow-up. Samples should be taken from the contralateral arm to the infusion. Pre-dose PK must be taken within 2 hours prior to the start of avelumab infusion, but before any drug (i.e. entinostat) is given. Post-dose PK must be taken within 6 minutes from the end of infusion.

[22] Samples for avelumab ADA will be taken pre-dose (within 2 hours prior to the start of avelumab infusion, but before any drug (i.e. entinostat) is given); Day 1 of Cycles 1 thru 6, then cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and 30-day Safety Follow-up. Samples positive for ADA may also be tested for neutralizing antibodies. Samples should be taken from the contralateral arm to the infusion.

[23] All procedures listed in the above table will be done for patients in both the Phase 1b and Phase 2.

2. STUDY GLOSSARY

Abbreviation/Acronym	Definition
AdaM	Analysis Dataset Model
ACTH	adrenocorticotropic hormone
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
[redacted]	[redacted]
CBR	clinical benefit rate
CI	confidence interval
C_{min}	minimum trough concentration
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
C_{trough}	trough concentration
CYP	Cytochrome P
DC	dendritic cell
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee

Abbreviation/Acronym	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FDG	18F-deoxyglucose
FOLFOX	folinic acid, 5-fluorouracil, and oxaliplatin
FoxP3	Forkhead box P3
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
G-MDSC	granulocyte myeloid-derived suppressor cells
H2	histamine receptor agonists
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDAC	histone deacetylase
HEENT	head, ears, eyes, nose, and throat
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IFN-γ	interferon-gamma
Ig	immunoglobulin
IL	interleukin
INR	International Normalized Ratio

Abbreviation/Acronym	Definition
IP	intraperitoneal
irAE	immune-related adverse events
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
K_M	Michaelis-Menten constant
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PARP	poly-ADP ribose polymerase
PBMC	peripheral blood mononuclear cell
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
P-gp	permeability glycoprotein
PK	pharmacokinetic
PLD	pegylated liposomal doxorubicin
PMN	polymorphonuclear
PO	orally

Abbreviation/Acronym	Definition
PR	partial response
PT	prothrombin time
RANKL	receptor activator of nuclear factor-κB ligand
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommend Phase 2 dose
RSE	relative standard error
SD	standard deviation
SDTM	Study Data Tabulation Model
$t_{1/2}$	half-life
T4	thyroxine
TCR	tissue cross reactivity
T_{EM}	T cells with an effector memory
TGF	transforming growth factor
TNF	tumor necrosis factor
TO	target occupancy
Tregs	regulatory t cells
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
V_{max}	maximal elimination
WBC	white blood cell (count)

3. BACKGROUND AND RATIONALE

3.1 Epithelial Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease (Fleming 2009). Although expectations for long-term survival can be very high if the cancer is identified and treated early, women diagnosed with advanced ovarian cancer continue to have a 5-year survival rate of less than 30% (American Cancer Society 2015).

Ovarian neoplasms consist of several histopathological entities. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 80%; Chan 2006); however, other less common pathologic subtypes must be considered in treatment recommendations.

3.2 Treatment of Epithelial Ovarian Cancer

Treatment of ovarian cancer represents a significant challenge due to the median age at the time of diagnosis (63 years), and the fact that the majority of cases are diagnosed in an advanced stage. Aggressive chemotherapeutic agents can be difficult for older patients to tolerate, particularly in conjunction with concomitant medications and comorbidities. Frequently, these patients have declining performance status and bowel dysfunction.

A combination of taxane and platinum-based chemotherapy is standard first-line treatment for ovarian cancer following surgical intervention (Troso-Sandoval 2015). Drugs that have demonstrated activity in ovarian cancer include taxanes (paclitaxel, docetaxel, nab-paclitaxel), topoisomerase 1 and 2 inhibitors (topotecan, liposomal doxorubicin, and etoposide), epothilones (ixabepilone and ZK-EPO), alkylators (hexamethymelamine and ifosfamide), and antimetabolites (pemetrexed and gemcitabine) (Markman 2000). Effective treatment regimens include intravenous (IV) paclitaxel administered every 3 weeks in combination with carboplatin; weekly administration of paclitaxel in combination with carboplatin; or IV and intraperitoneal (IP) paclitaxel and IP cisplatin.

Patients are considered to have platinum-sensitive disease if they respond to first-line platinum therapy and experience a relapse-free period of greater than 6 months following the last dose of platinum therapy. Platinum-resistant disease is defined by relapse between 0 to 6 months after the last platinum dose. Platinum-refractory disease is defined by lack of response to platinum-based chemotherapy or recurrence prior to completion of platinum-based therapy (Markman 2000).

There are no highly effective therapies in the platinum-resistant/refractory population, although non-platinum-related agents have demonstrated modest antitumor efficacy in a subset of these patients. For management of resistant disease, drugs that have demonstrated activity in ovarian cancer are used as single agents in sequence and have demonstrated response rates in the range of 10% to 20% with median times to progression of 3 to 4 months (Markman 2000).

In 2014, bevacizumab plus chemotherapy was approved in European Union (EU) and United States (US) in combination with paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan, for the treatment of patients with platinum-resistant recurrent ovarian cancer. This approval was based on results of the AURELIA study, which randomized patients to physician's choice of chemotherapy (PLD, paclitaxel, or topotecan) with or without bevacizumab, and included patients with more than one prior line of platinum based chemotherapy. This study demonstrated improvement in median progression-free survival (PFS) from 3.4 months to 6.7 months (hazard ratio [HR] = 0.48, 95% confidence interval [CI]: 0.38 to 0.60, $p < 0.001$). No statistically significant improvement in overall survival (OS) was seen (Pujade-Lauraine 2014). In 2014, olaparib, a poly-ADP ribose polymerase (PARP) inhibitor, was approved for the treatment of patients with advanced Breast Cancer Antigen-mutated ovarian cancer by European Medicines Agency (EMA) and Food and Drug Administration (FDA; Kaufman 2014).

3.3 The Role of Immuno-oncology

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 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) cells 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 checkpoint proteins, such as programmed cell death protein ligand 1 (PD-L1) and programmed cell death protein ligand 2 (PD-L2), which 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).

Investigations of the limited efficacy of recently developed immune therapies has provided insight into the role that specific immune regulatory cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), have in dampening the cytotoxic T cell response (Joyce 2015; Mahoney 2015; Sharma 2015). Myeloid-derived suppressor cells and Tregs localize in the area surrounding the tumor and, together with the immune checkpoints, play a significant role in helping a tumor evade detection and elimination by the immune system (Adeegbe 2013; Marvel 2015).

Myeloid-derived suppressor cells are immature myeloid cells 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 to a poor prognosis and limited response to cancer therapy (Liu 2010; Solito 2011; Najjar 2013; Weed 2015). 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).

Regulatory T cells, a second type of immune suppressor cell, are recruited to sites of active immune response to shut down the cytotoxic T cell response. 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). Regulatory T cells 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.

3.4 Study Rationale

The cell surface checkpoint protein PD-L1 (also called B7-H1 or CD274) and its receptor, PD-1, have a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell function (Ascierto 2010; Riley 2009; Fife 2011).

Tumors including ovarian cancer present with various rates of somatic (or genetic) mutations (Kandoth 2013; Lawrence 2013). These genetic alterations result in expression of proteins that are “different from self” on cancer cells which may act as antigens enhancing the ability of the host immune system to recognize tumor cells as foreign and stimulate T cell response (Chen 2013). However, tumors elude immune surveillance through the expression of PD-L1 in

the tumor microenvironment (Liotta 2010). Several antibodies blocking PD-1 and PD-L1 demonstrated significant and durable response in patients with cancer (Zamarin 2015).

A nonclinical study assessed the effects of immune checkpoint inhibitors alone and combined with other agents in BALB/c mice bearing CT26 and 4T1 tumors (Kim 2014). CT26 and 4T1 are syngeneic murine tumor models commonly used for the assessment of novel therapeutic approaches. The CT26 model is considered to be modestly immunogenic whereas the 4T1 model is poorly immunogenic and highly metastatic. In the CT26 model, treatment with immune checkpoint-blocking antibodies, either anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) or anti-PD-1, resulted in retardation of tumor growth but not tumor eradication. Furthermore, treatment with either antibody resulted in tumor eradication in the vast majority of mice with moderately-sized tumors (~400 mm^3), but not with tumors > 600 mm^3. In BALB/c mice bearing 4T1 tumors, limited response was seen to treatment with either anti-PD-1 or anti-CTLA-4 antibodies.

Functional studies revealed that the primary targets of epigenetic modulation were MDSCs, which are often elevated in tumor-bearing hosts and have potent immunosuppressive activities. Specifically, treatment of granulocytic MDSCs (G-MDSCs) with entinostat in vitro resulted in markedly reduced viability in a dose-dependent fashion. Importantly, entinostat had only modest effects on CD8+ T cells, creating a large therapeutic window in which G-MDSCs can be depleted while sparing CD8+ T cells.

When co-cultured with CD8+ T cells, G-MDSCs inhibited interferon-gamma (IFN-γ) secretion. However, when entinostat was included in the culture medium, entinostat reverted this inhibition in a dose-dependent manner. These data support the premise that G-MDSCs directly inhibit the function of CD8+ T cells and that entinostat alleviates this inhibition by directly suppressing G-MDSCs.

Avelumab (MSB0010718C), a fully human antibody of the immunoglobulin (Ig) G1 isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity (Avelumab Investigator's Brochure [IB] 2016). Preliminary data from the ongoing ovarian

cancer avelumab monotherapy Study EMR 100070-001 showed an overall response rate (ORR) of 10.7% and stable disease in an additional 44% of patients with advanced ovarian cancer.

Combining avelumab with epigenetic agents might increase tumor immunogenicity and responsivity to checkpoint inhibition through manipulation of the tumor microenvironment. Co-treatment with epigenetic-modulating drugs and checkpoint inhibitors was showed to markedly improve responses and survival in preclinical modestly immunogenic or metastatic tumor models. Functional studies revealed that the primary targets of the epigenetic modulators were myeloid-derived suppressor cells, suggesting that cancers resistant to immune checkpoint blockade can be cured by eliminating MDSCs. In particular, the addition of azacitidine and entinostat to anti-CTLA-4 and anti-PD1 reduced Ly6G+ circulating G-MDSCs. These results therefore indicated an additional mechanism of action of deoxyribonucleic acid (DNA)-methyltransferase and histone deacetylase (HDAC) inhibitors: these agents also act on host cells in the immune system such as MDSCs (Kim 2014).

In consideration of clinical and nonclinical findings, it is hypothesized that entinostat combined with a PD-1/PD-L1-blocking antibody (i.e., avelumab) will result in an improved response rate for the combination compared to either agent alone.

3.5 Study Treatment

3.5.1 Entinostat (SNDX-275)

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

Deoxyribonucleic acid 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.

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 inhibited HDAC in various tumor cell lines. In particular, entinostat induced accumulation of acetylated histones adjacent to the promoter of the transforming growth factor (TGF)-β type II receptor gene, with resulting gene expression. Mutations affecting the TGF-β signaling pathway have been associated with development and progression of human malignancies, including carcinomas of the lung, breast, prostate, and colon. 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 xenografts, including models of 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, or progenitor cell pool and potential sensitization to subsequent post-study treatments (Juergens 2011).

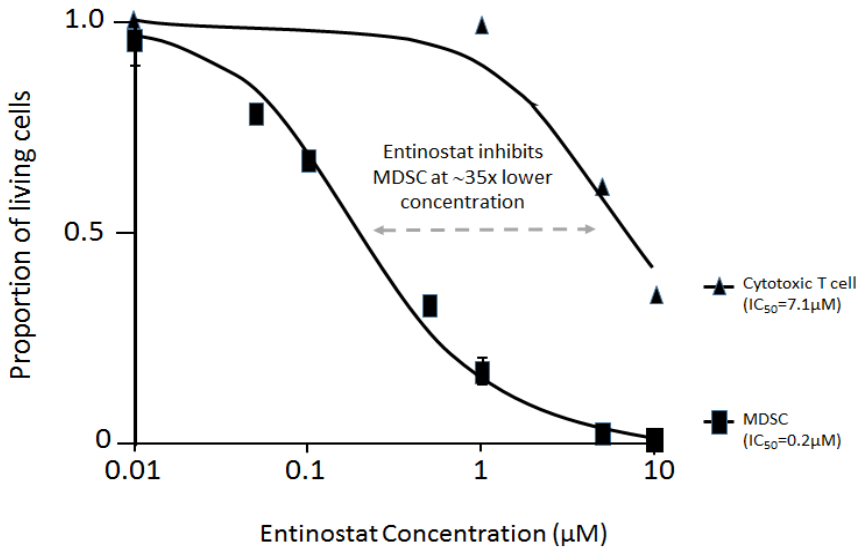
Additional information on the chemistry, pharmacology, toxicology, preclinical findings, and clinical experience to date may be found in the Entinostat IB.

3.5.1.1 Preclinical Studies of Entinostat

Preclinical studies have demonstrated that entinostat is a dual inhibitor of immune suppressor cells targeting MDSCs and Tregs. Entinostat reduces the growth of MDSCs at concentrations that spare the growth of cytotoxic T cells (Figure 3-1). Approximately half of the MDSCs are stopped from growing at 200 nM of entinostat, which is 35 times less than the concentration of entinostat required to stop half of the cytotoxic T cells from growing (Kim 2014).

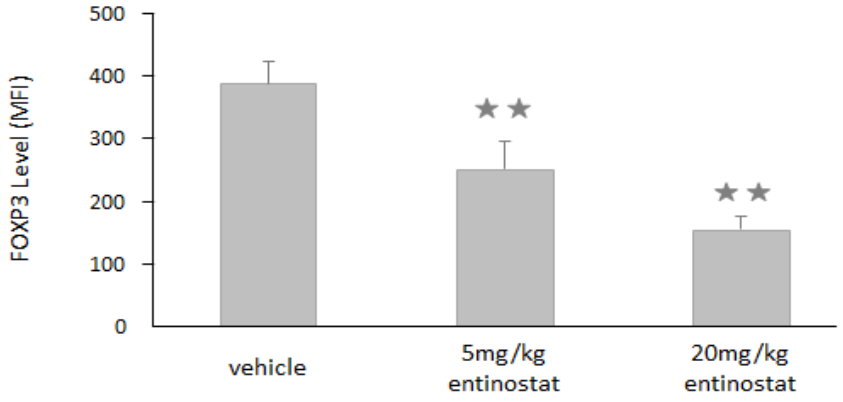
Previous research has demonstrated that Forkhead box P3 (FOXP3), a protein involved in Treg function, is an indicator of Treg immune suppressor activity. Entinostat reduces the expression of FOXP3 protein in Tregs, when administered in an animal cancer model, thus demonstrating the ability of entinostat to inhibit Treg immune suppressor activity (Figure 3-2; Shen 2012).

Figure 3-1. Entinostat Inhibition of Myeloid-derived Suppressor Cells



MDSC = myeloid-derived suppressor cells
Source: Kim, 2014

Figure 3-2. Entinostat Reduces the Expression of FOXP3 Protein in Tregs

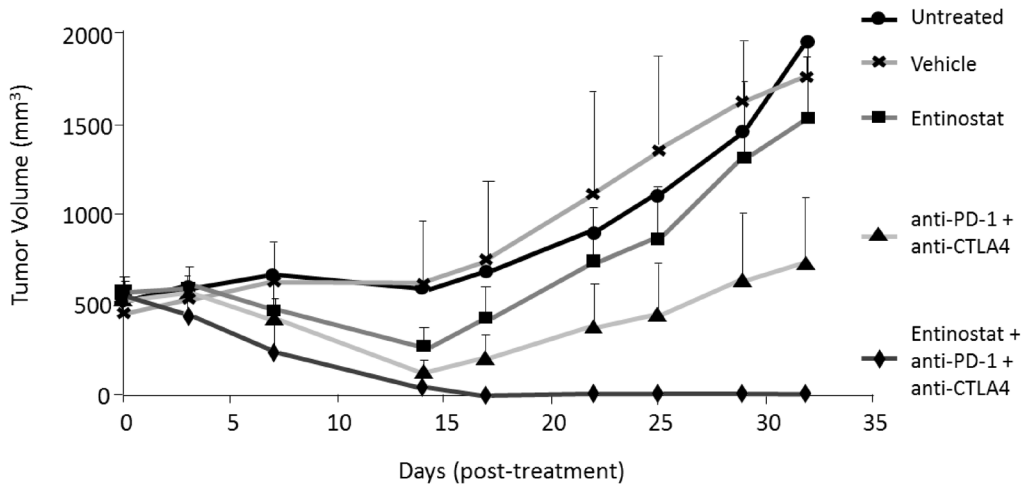


MFI – mean fluorescence intensity is a unit of measurement of FOXP3 protein

Source: Shen, 2012

Entinostat was tested in combination with anti-PD-1 and anti-CTLA-4-directed antibodies in immune-resistant animal models to determine whether entinostat could be combined effectively with immune checkpoint inhibitors. 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/CTLA-4 checkpoint inhibition (Figure 3-3). This experiment demonstrated 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 avelumab in TNBC.

Figure 3-3. The Elimination of Primary and Metastatic Tumors in a Mouse Breast Cancer Model Treated with Entinostat in Combination With Dual PD-1/CTLA-4 Checkpoint Inhibition



CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; PD-1 = programmed death receptor-1
Source: Kim 2014

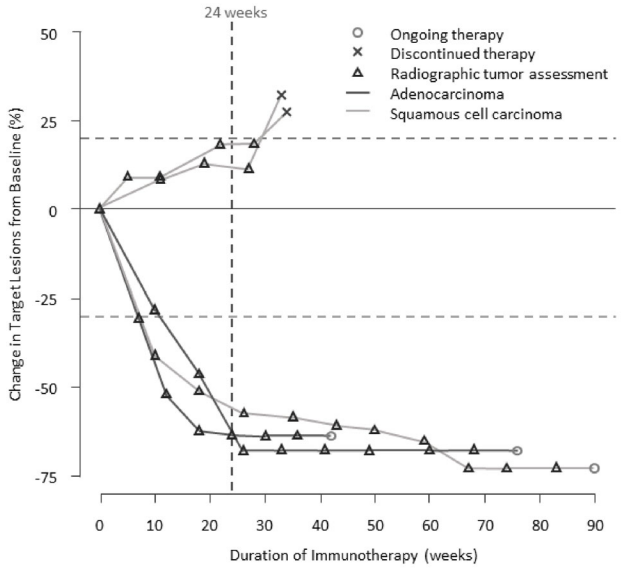
3.5.1.2 Clinical Studies of Entinostat

To date, entinostat has been investigated alone and in combination in more than 900 patients with cancer in clinical studies. Entinostat was well tolerated at the doses and schedules investigated. The adverse events reported most frequently included gastrointestinal 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. More information can be found in the Entinostat IB.

Two clinical trials at Johns Hopkins University demonstrated preliminary evidence for the potential beneficial effects of combining entinostat with a PD-1 or PD-L1 inhibitor. In a heavily pre-treated metastatic non-small-cell lung cancer (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. All 5 patients who received either nivolumab, an approved anti-PD-1, or an investigational PD-L1 inhibitor as their next therapy derived durable clinical benefit (Figure 3-4). Three of the patients had durable responses and 2 had durable stable disease. This enhanced response rate was better than the 15% response to nivolumab alone observed in a similar advanced NSCLC population, leading investigators to hypothesize that the prior effect of the combination of entinostat and azacitidine therapy was "priming" the tumors for 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 Johns Hopkins University have initiated a follow-on randomized Phase 2 clinical trial, J1353.

Figure 3-4. Patients Who Received Nivolumab or an Investigational PD-L1 Inhibitor as Secondary Therapy Derived Durable Clinical Benefit

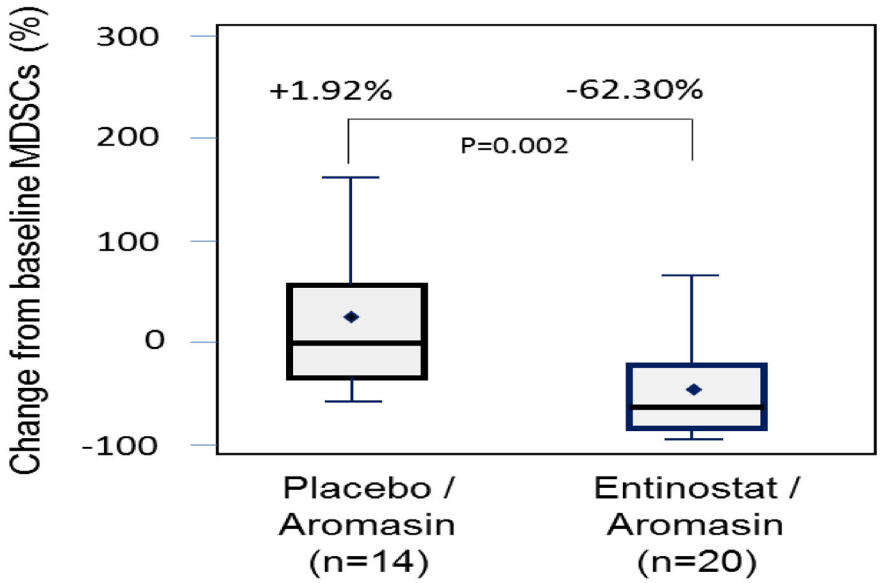


Data on file

In a randomized, placebo-controlled Phase 2b clinical trial, ENCORE 301 (Yardley 2013), entinostat was studied in combination with hormonal therapy (exemestane) in advanced ER+ breast cancer patients. Whereas only a modest benefit in PFS was observed for patients

receiving entinostat (median of 4.3 months vs. 2.3 months for those receiving placebo), a marked overall survival benefit was observed (median of 28.1 months vs 19.8 months). An analysis of immune cells was conducted with blood samples collected from a subset of these patients. A statistically significant reduction in the concentration of circulating MDSCs was observed in patients treated with the combination of entinostat + exemestane, but not in patients treated with the combination of placebo + exemestane (Figure 3-5).

Figure 3-5. Entinostat Reduces MDSCs in Peripheral Blood Samples



Aromasin = exemestane; MDSC = myeloid-derived suppressor cell
Data on file

Based on these findings it is hypothesized that entinostat combined with avelumab will result in an improvement in PFS for the combination compared to avelumab alone.

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

3.5.2 Avelumab

Avelumab (also referred to as MSB00104718C) is a fully human antibody of the IgG1 isotype with a molecular weight of 143,832 Dalton. It is produced by mammalian cell culture in a serum-free growth medium. Avelumab binds PD-L1 and blocks the interaction between PD-L1

and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response (Avelumab IB 2016)

The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions (Chemnitz 2004; Keir 2008; Avelumab IB 2016). PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; PD-L1 expression is greatly up-regulated after activation or interferon treatment (Keir 2008). Numerous results from in vitro cellular assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production (Dong 1999; Freeman 2000; Bennett 2003; Brown 2003; Blank 2004; Blank 2006; Wackerle-Men 2007). In PD-1–/– mice, both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies (Okazaki 2006; Okazaki 2007). Breaking tolerance through blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer (Blank 2005).

External and internal immunohistochemistry studies have demonstrated that PD-L1 is also expressed by a variety of human tumors, both by the tumor cells as well as the immune cells that are present in the tumor microenvironment (Okazaki 2007). In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue (Brown 2003). High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers (Okazaki 2007). Importantly, anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in combination therapy setting (Zou 2016).

Given the important role of PD-L1 in the suppression of T-cell responses and the mode of action of avelumab, which blocks the interaction between PD-L1 and its receptors, avelumab is being developed as a potential therapy for subjects with various tumors.

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

3.5.2.1 Preclinical Studies

The nonclinical strategy of the avelumab 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 1 starting dose.

Nonclinical Pharmacology

Nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo. As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 μg per dose (~20 mg/kg) was identified as the optimally effective dose when given every third day for a total of 3 doses.

The in vivo anti-tumor effects were primarily mediated by CD8+T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of antibody-dependent cell-mediated cytotoxicity (ADCC) as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment crystalline receptor binding or via the systemic depletion of NK cells. In both settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX]), and radiation therapy demonstrated better tumor growth inhibition. In particular, radiation therapy was a highly synergistic combination with avelumab, capable of causing complete regression of established tumors probably through generating anti-tumor immune memory.

Treatment with avelumab resulted in a consistent increase in the percentage of CD8+PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (T_{EM}) phenotype

as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T-cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in CD8+PD-1+ T cells, CD8+ T_{EM} cells, and antigen-specific T-cell responses, may be leveraged as pharmacodynamics biomarkers with translational relevance to the clinical setting.

Nonclinical Pharmacokinetics and Metabolism

Avelumab demonstrated pronounced non-linear PK characteristics in mice and monkeys in single-dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Toxicokinetic data from repeated dose toxicity studies in mice, rats, and monkeys indicated that the PK of avelumab was linear within the dose range of 20 to 140 mg/kg, suggesting that the target mediated clearance could be saturated when higher doses than 20 mg/kg are administered. Similar terminal half-lives ($t_{1/2}$) of approximately 60 to 70 hours were observed in toxicity studies in mice and monkeys.

A PK/pharmacodynamics study in C57BL/6 mice was used to correlate receptor occupancy data of avelumab in blood with drug concentrations. A plasma concentration of 58.5 μg/mL was calculated as required for 95% target occupancy (TO) in this model.

Nonclinical Toxicology

The toxicological profile of avelumab was evaluated in repeat-dose, 4-week toxicity studies with once weekly IV bolus injection/infusion of avelumab in mice, rats, and cynomolgus monkeys; a repeat-dose toxicity study with intermittent once weekly IV infusion of avelumab over 13 weeks followed by an 8-week recovery period in cynomolgus monkeys; in vitro cytokine release assays in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs); and tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues. Initial cytokine release assays in human and cynomolgus monkey whole blood and PBMCs revealed no evidence for release of pro-inflammatory cytokines. However, a

subsequent, optimized cytokine release assay demonstrated evidence of potential cytokine release in phytohemagglutinin pre-stimulated PBMCs.

On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. Due to severe hypersensitivity reactions after repeated administration of avelumab in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) is applied.

In cynomolgus monkeys, no clinical signs of hypersensitivity were observed in the pilot 4-week IV repeat-dose toxicity study or in the pivotal 13-week study after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg. A no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established in both studies.

3.5.2.2 Clinical Studies

Avelumab is currently being tested as monotherapy and in combination therapies in multiple Phase 1, 2, and/or 3 studies with over 1400 patients treated in solid tumors (see Avelumab IB 2016 for study descriptions). Safety data suggest an acceptable toxicity profile for avelumab. Most of the observed events were either consistent with those expected in subjects with advanced solid tumors or with similar class effects of monoclonal antibody (mAb) blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

A Phase 3 global study is currently being conducted to determine whether avelumab administered alone or in combination with PLD is superior to PLD alone in prolonging overall survival in patients with platinum-resistant or refractory ovarian cancer. A second Phase 3 study is designed to demonstrate whether avelumab given as single agent in the maintenance setting following frontline chemotherapy or in combination with carboplatin/paclitaxel is superior to platinum-based chemotherapy alone followed by observation in newly diagnosed ovarian cancer patients (Clinicaltrials.gov).

Avelumab in Ovarian Cancer

The Phase 1 Trial EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004), is an open-label, multiple ascending dose trial designed to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. The ovarian cancer expansion cohort enrolled and treated a total of 75 patients. This cohort consisted of subjects with recurrent or refractory ovarian cancer who had progression within 6 months of platinum-based therapy or subjects who previously relapsed with progression after subsequent therapy. The ovarian cancer expansion cohort of the study had a data cutoff approximately 13 weeks after the start of avelumab treatment for the last subject who was included in this pre-planned interim analysis. The ORR based on confirmed and unconfirmed responses for subjects treated in this cohort was 10.7% (8 of 75 subjects). In 5 of the 8 responders (62.5%), the responses were ongoing at the time of the data cutoff. The onset of the response was at approximately 6 weeks in 4 subjects. The onset of response for the 4 other responders occurred at Weeks 10, 11, 14, and 18, respectively. The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% CI: 6.3 to 12.0 weeks; Disis, 2015). As of 13 February 2015, a total of 54 events (progressive disease [PD] or death) had occurred. The Kaplan-Meier estimates predicted a PFS rate of 34.5% and 17.2% at 12 and 24 weeks, respectively.

Avelumab in Non-small Cell Lung Cancer

The NSCLC expansion cohort in the ongoing Phase 1 Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after the start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). This group of NSCLC subjects presented with a median age of 65.0 years, and all of whom had Stage IIIB or IV NSCLC that had progressed after at least 1 line of platinum-containing doublet chemotherapy for metastatic or locally advanced disease. At the time of the data cutoff, 41 of 184 subjects (22.3%) remained on treatment, and 143 subjects (77.7%) discontinued treatment, primarily due to disease progression (93 subjects, 50.5%), and adverse event(s) (17 subjects, 9.2%). The median avelumab treatment

duration in the NSCLC expansion cohort was 12.2 weeks (range: 2 to 64 weeks), and the median number of avelumab infusions received was 6.0 (range: 1 to 29). For the primary efficacy analysis of the NSCLC expansion cohort, the confirmed best overall response included 1 complete response (CR) and 20 partial responses. Therefore, the confirmed ORR was 12.0%, (22 of 184 subjects; 95% CI: 7.6% to 17.5%). The median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

Avelumab in Gastric Cancer

The ongoing Phase 1 Trial EMR 100070-002 was designed to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with an expansion cohort in subjects with gastric cancer. The preliminary efficacy data for the ongoing Phase 1 Trial EMR 100070-002 are based on 20 Japanese subjects being treated with 10 mg/kg of avelumab once every 2 weeks in the gastric cancer expansion cohort. All subjects had received at least 1 line of anti-tumor therapy for locally advanced or metastatic tumor before enrollment, and 75% of the subjects (15 of 20) received 2 or more prior therapies. As of the data cutoff of 11 March 2015, all subjects were observed for a minimum follow-up of 13 weeks. The median duration of avelumab treatment was 12.0 weeks (range: 4 to 29 weeks) and the median number of avelumab infusions was 6.0 (range: 2 to 13). Three of 20 subjects (15.0%) remained on treatment and 17 of 20 subjects (85%) discontinued treatment at the time of the data cutoff, mainly due to disease progression (14 subjects, 70%), or adverse event(s) (2 subjects, 10%). Three of 20 subjects responded to treatment (all confirmed PRs), and the best overall response was 15.0% (95% CI: 3.2% to 37.9%). First response was at approximately Week 6 for 2 responders and at approximately Week 18 for 1 responder. Two of the 3 responders remained in response at the time of the data cutoff. The median PFS was 11.9 weeks (95% CI: 6.0 to 12.3 weeks; Avelumab IB 2016).

3.6 Rationale for the Dose Selection

3.6.1 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 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 maximum-tolerated dose (MTD) for single-agent entinostat in non-hematologic indications was established as 4 mg/m^2 weekly for 3 weeks, followed by a 1 week rest, or 10 mg/m^2 every other week continuously.

Pharmacokinetic analyses have demonstrated approximately 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 was tolerated well when given once weekly continuously at a dose of 5 mg (in combination with the aromatase inhibitor exemestane) to patients with locally advanced or metastatic breast cancer or every other week continuously at a dose of 10 mg (in combination with erlotinib) to patients with Stage IIIB/IV NSCLC. The adverse event profiles at these dose schedules were consistent with previous clinical experience, with the most common adverse events being fatigue and gastrointestinal disturbances (nausea, vomiting, and diarrhea).

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

3.6.2 Avelumab

The dose of avelumab selected for the currently ongoing and future additional clinical trials is 10 mg/kg administered IV once every 2 weeks. This dose was selected after review of the PK,

pharmacodynamics, receptor occupancy, and preliminary clinical safety and efficacy data observed in the ongoing Phase 1 Trial EMR 100070-001.

Avelumab plasma levels leading to full TO on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a pharmacodynamic marker for the ability of avelumab to act on its target and to show clinical activity. Target occupancy on peripheral blood CD3+ T-cells was therefore investigated in human blood in vitro by flow cytometry and a plateau indicating at least 95% receptor occupancy was reached in all blood samples at an avelumab concentration of 1 µg/mL.

Pharmacokinetic profiles obtained during the dose-escalation phase of Trial EMR 100070-001 were used to determine if a concentration of at least 1 µg/mL was achieved throughout the dosing interval. The median (± standard deviation [SD]) trough concentration (C_{trough}) at the end of the first cycle after administration of the 10 mg/kg dose was 21 µg/mL (± 12 µg/mL; n = 283). The median C_{trough} increased during subsequent cycles: second cycle: 25 µg/mL (± 16 µg/mL; n = 269); third cycle: 27 µg/mL (± 17 µg/mL; n = 202), and remained between 27 and 36 µg/mL during subsequent cycles (n = 55 to 171).

These data were confirmed in ex vivo samples taken at minimum trough concentration (C_{min}) after the first dose (Day 15) in a small number of subjects during the initial dose escalation portion of the Phase 1b Trial EMR 100070-001 (n = 9). For doses of 10 mg/kg, TO for 4 subjects was > 90% at trough serum levels ranging from 12.69 to 26.87 µg/mL. For doses of 3 mg/kg, available TO data for 2 subjects with trough levels ranging from 4.56 to 6.99 µg/mL showed > 90% TO at trough exposure levels; at 1 mg/kg, 2 of 3 subjects displayed < 90% TO at trough serum concentrations. Avelumab serum concentrations were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Further evidence for full TO achieved with the 10 mg/kg dose throughout the entire dosing interval was derived from the population PK model based on data from 410 subjects in studies EMR 100070-001 and EMR 100070-002. Eighty-three subjects with rich PK profiles, 9 subjects with peak and trough concentrations and 318 subjects with only trough concentrations were included in this analysis. A 2-compartment model with mixed linear plus Michaelis-

Menten elimination was evaluated. Limited by very few observations collected in the low concentration range showing non-linear elimination, a Michaelis-Menten elimination was only observed at very low concentrations (V_{max}) [maximal elimination] = 0.07 mg/h; [relative standard error {RSE} = 94%]; Michaelis-Menten constant (K_M) = 0.9 µg/mL [RSE = 448%]).

Based on these results, it can be assumed that at doses of 10 mg/kg and greater, administered every 2 weeks, a high TO is achieved in subjects throughout the entire dosing interval.

3.7 Summary of Benefit/Risk Assessment

This clinical trial will be conducted in compliance with the clinical trial protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and the applicable national regulatory requirements.

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the nonclinical and Phase 1 data available to date, the conduct of the trial is considered justifiable using the dose and dose regimen of avelumab and entinostat as specified in this clinical trial protocol. A data safety monitoring board (DSMB; see Section 12.6) will assess the risk-benefit ratio on an ongoing basis. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk benefit relationship that would render continuation of the trial unjustifiable.

3.7.1 Avelumab

Available adverse event and laboratory abnormality data from patients with advanced solid tumors treated with single-agent avelumab suggest an acceptable safety profile of the compound with over 1400 patients treated in solid tumors. The most frequently reported adverse events for patients treated with avelumab include fatigue, gastrointestinal disturbances, infusion-related reactions, decreased appetite, anemia, cough, dyspnea, fever, and chills. Adverse events ≥ Grade 3 in severity occurred in 9.5% of patients and the incidence of individual reported adverse events ≥ Grade 3 were rare (< 1 %). Most of the observed events were either in alignment with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions

including hypersensitivity and immune-related adverse events/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include a treatment algorithm and guidelines for treatment interruption and discontinuation in case of immune-related adverse events, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen. Avelumab demonstrated clinical activity in heavily pretreated ovarian cancer patients in an expansion cohort of an ongoing Phase 1 study.

3.7.2 Entinostat

Entinostat has been evaluated as monotherapy and in combination with other agents in more than 900 patients with cancer in 29 clinical studies, of which 6 are active. Across indications and regimens, the most commonly reported adverse events in entinostat-treated patients include fatigue, gastrointestinal disturbances, and hematological abnormalities. Fatigue is the most consistently reported adverse event associated with entinostat. Fatigue tended to occur early and be variable in duration. Fatigue was often, but not consistently accompanied by anemia, which also was more prevalent in the entinostat group relative to placebo. Overall, fatigue was tolerable.

Neutropenia has been encountered commonly with entinostat. Neutropenia tended to occur later in treatment and in patients with disease in the bone, but was not complicated by fever or infection. Thrombocytopenia is considered a class effect with HDAC inhibitors and appears to be due to an effect on platelet maturation and release as opposed to myelosuppression, a cytotoxic effect on megakaryocytes, or the half-life of circulating platelets (Bishton 2011). The incidence of thrombocytopenia (all severities) varied markedly across entinostat studies, and the incidence of Grade 3 or 4 thrombocytopenia was disparate. Thrombocytopenia tended to be more common and more severe in patients with hematologic malignancies relative to patients with solid tumors and higher with certain drug combinations.

The most commonly reported adverse events in patients with solid tumors given entinostat monotherapy included hypoalbuminemia, fatigue, nausea, hypophosphatemia, anemia, and

thrombocytopenia. Hypoalbuminemia and hypophosphatemia were seen at higher incidences in patients with solid tumors receiving entinostat monotherapy than in those with hematologic malignancies; this may be related to the advanced disease of the population.

3.7.3 Avelumab and Entinostat Combination Therapy

Overall, the adverse event profile of entinostat when given in combination was similar to that seen when given as monotherapy, with the most commonly reported adverse events (regardless of tumor type) being fatigue, nausea, anemia, thrombocytopenia, leukopenia, diarrhea, neutropenia, and vomiting. As would be expected, the adverse event profile of entinostat when given in combination varied somewhat based on the combination agent and the corresponding patient population. For patients treated with avelumab, the most frequently reported adverse events include fatigue, gastrointestinal disturbances, infusion-related reactions, decreased appetite, anemia, cough, dyspnea, fever, and chills. Therefore, potential overlapping toxicities include fatigue and gastrointestinal disturbances. For both entinostat and avelumab, the majority of adverse events were Grade 1 or 2 in severity and are not anticipated to present a significant safety concern.

Based on the clinical and nonclinical findings described in Section 3.5, it is hypothesized that entinostat combined with avelumab will result in a tolerable safety profile and an improved response rate for the combination compared to either agent alone in this advanced ovarian cancer patient population.

4. OBJECTIVES

4.1 Primary

The primary study objectives are:

Phase 1b/Safety Lead-in: To determine the DLT and MTD or recommended Phase 2 dose (RP2D) of entinostat (SNDX-275) given in combination with avelumab.

Phase 2/Expansion Phase: To perform an evaluation of the efficacy of entinostat in combination with avelumab at the RP2D versus avelumab plus placebo in patients with refractory or recurrent epithelial ovarian cancer, as determined by the duration of PFS based on the local investigator's assessment of progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

4.2 Secondary

The secondary study objectives are:

Efficacy: To evaluate the efficacy of entinostat in combination with avelumab in patients with advanced epithelial ovarian cancer, as determined by:

- Progression-free survival based on immune-response RECIST (irRECIST)
- Overall response rate (i.e., CR or PR) based on RECIST 1.1 and irRECIST
- Clinical benefit rate (CBR) (i.e., CR or PR or stable disease for at least 24 weeks) based on RECIST 1.1 and irRECIST
- Overall survival

In patients with best overall confirmed response of CR or PR:

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

Pharmacokinetics: To assess the effect of entinostat on the PK of avelumab

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

4.3 Exploratory

[redacted]

4.4 Hypothesis

Phase 1b: The combination of avelumab and entinostat at a biologically active dose will be safe and warrants further investigation in additional patients.

Phase 2: Entinostat combined with avelumab at the dose determined in Phase 1b will result in an improved PFS compared to avelumab alone.

5. ENDPOINTS

5.1 Efficacy

The primary efficacy endpoint of the study is PFS, as determined by the local investigator using RECIST 1.1

Secondary endpoints:

- Progression-free survival determined by the local investigator using irRECIST
- Overall response rate (CR or PR) by RECIST 1.1 and irRECIST
- Clinical benefit rate (CR, PR, or stable disease for at least 24 weeks) by RECIST 1.1 and irRECIST
- Overall survival
- Duration of response and TTR (in patients who experience best overall response of CR or PR)
- The effect of entinostat on the PK of avelumab

5.2 Safety

Safety endpoints are:

- Determination of DLT, MTD, and RP2D
- Incidence of treatment-emergent adverse events, serious adverse events, adverse events resulting in the permanent discontinuation of study drug, and deaths occurring within 30 days of the last dose of study drug
- Change from baseline in vital signs, ECOG, physical examination, electrocardiograms (ECGs), and laboratory assessments

5.3 Exploratory

[redacted]

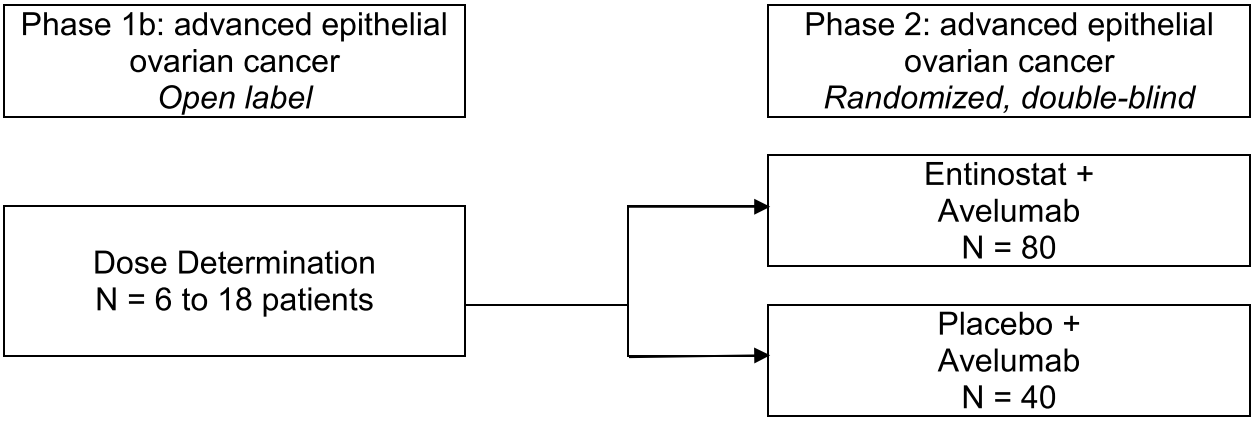
[redacted]

6. EXPERIMENTAL PLAN

6.1 Study Design

Study SNDX-275-0603 is a randomized, placebo-controlled, double-blind, multicenter Phase 1b/2 study evaluating the combination of entinostat plus avelumab in patients with advanced epithelial ovarian cancer. The study has 2 phases: an open-label Safety Lead-in (Phase 1b) followed by an Expansion Phase (Phase 2) (Figure 6-1).

Figure 6-1: Study Schema



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 days of starting study treatment on Cycle 1, Day 1.

A cycle is 14 days in length. During treatment, patients will attend study center visits for study evaluations on Days 1 and 8 of Cycles 1 and 2, and on Day 1 of each cycle thereafter. Patients will have radiological disease assessments performed within 28 days prior to enrollment, then every 6 weeks (± 3 days) when measured from Cycle 1, Day 1, during study treatment through Week 36 (i.e., Weeks 6, 12, 18, 24, 30, 36) until unequivocal PD per RECIST 1.1. Patients remaining on study after Week 36 will undergo radiological disease assessments every 8 weeks (± 3 days) until unequivocal PD occurs. Disease will be assessed by computed tomography (CT) and magnetic resonance imaging (MRI), as appropriate, using the same method used for the

screening evaluation, and response will be assessed by the investigator using RECIST 1.1 and irRECIST.

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

- Availability of a recent formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from a de novo tumor biopsy during screening. If patients whose only accessible lesion for biopsy is a solitary target lesion, it must be amenable to a core biopsy that will not compromise assessment of tumor measurements. Alternatively, a recently obtained archival FFPE tumor tissue block (cut slides not acceptable) from a primary or metastatic tumor resection or biopsy can be provided if the biopsy or resection was performed within 1 year of randomization or if biopsy is clinically contra-indicated. Availability of an archival FFPE tumor tissue from primary tumor resection specimen (if not provided per above). If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.
- On Cycle 4 Day 1 (+ 3 days) on an optional basis from patients in the Safety Lead-in. All patients will be encouraged to provide an optional biopsy to help understand dose-immune correlate effects.
- On Cycle 4 Day 1 (+ 3 days) on an optional basis for patients in the Phase 2 portion who consent to biopsy
- 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, tumor tissue samples may be collected on a mandatory basis from all subsequent patients on Cycle 4 Day 1 (+ 3 days). Alternatively, if such data are not considered informative, these samples will not be collected from subsequent patients.

If the biopsy is performed and results are inconclusive or the sample is insufficient, patients may be asked for re-biopsy but it will not be mandatory.

Blood samples will be collected as follows:

- [redacted]
- [redacted]

- For determination of entinostat levels – pre-dose on Cycle 1 Day 1and 2 to 4 hours post-dose; anytime post-dose on Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 4 Day 1; and pre-dose on Cycle 2 Day 8.
- For determination of avelumab levels: pre-dose and at the end of infusion on Day 1 of Cycles 1 through 6, then Cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and at 30-day Follow-up. Pre-dose PK must be taken within 2 hours prior to the start of avelumab infusion, but before any drug (i.e. entinostat) is given. Post-dose PK must be taken within 6 minutes from the end of infusion.
- For determination of avelumab antidrug antibody (ADA neutralizing antibodies) levels: pre-dose on Day 1 of Cycles 1 through 6, then Cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and at 30-day Follow-up. Sample must be drawn within 2 hours prior to the start of avelumab infusion, but before any drug (i.e. entinostat) is given.
- For serum protein signatures - pretreatment on Cycle 1 Day 1 and Cycle 4 Day 1

Patients will remain on study treatment until unequivocal PD, intolerable toxicity, or one of the other study withdrawal criteria is met (Section 11). Patients with radiographic progression only, as defined by RECIST 1.1, should continue on study treatment until unequivocal PD is determined as defined by irRECIST, at the discretion of the investigator. After study treatment discontinuation, patients will complete an EOT visit within 7 days after the last study drug dose and 3 Safety Follow-up visits 30, 60 and 90 days (± 7 days) after the last EOT visit. The 60-day Safety Follow-up will be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care). Patients with ongoing toxicities will be followed more frequently per the Investigator's clinical judgement and standard of care. For example, Grade 3 or higher laboratory toxicities will be assessed at least weekly until resolution to Grade 2 or baseline grade. Entinostat and avelumab related toxicities will be managed as outlined in Section 9.10. The 90-day visit may also be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care) given that the patient's 90-day thyroid function tests are assessed locally.

After completion of the 30-day (± 7 days) Safety Follow-up visit, patients who have not experienced PD will be followed every 6 weeks for a clinic visit and radiological imaging until unequivocal PD or until study Week 36, whichever occurs first. If PD has not been documented at Week 36, patients will be followed every 8 weeks for radiological imaging until unequivocal PD, death, or end of the study, whichever occurs first. Following documentation of PD, patients

will be contacted every 3 months for documentation of survival status and post-study therapies until death or closure of the study by the Sponsor.

Phase 1b/Safety Lead-in (Dose Determination Phase):

Up to 18 patients evaluable for safety are expected to be enrolled in the Safety Lead-In/Dose Determination Phase of the study, which employs a rolling 6 Phase 1 trial design (Skolnik 2008). Two to 6 patients can be concurrently enrolled into a dose level, dependent upon: (1) the number of patients enrolled at the current dose level; (2) the number of patients who have experienced DLT at the current dose level; and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met.

For example, when 3 participants are enrolled onto a dose cohort, if toxicity data are available for all 3 when the 4th participant entered and there are no DLTs, the 4th participant is enrolled. If data are not yet available for 1 or more of the first 3 participants and no DLT has been observed, or if 1 DLT has been observed, the new participant is entered at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants 5 and 6. In place of suspending accrual after every 3 participants, accrual is only suspended when a cohort of 6 is filled. A participant who is inevaluable for toxicity will be replaced with the next available participant if de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study. Table 6-1 provides the decision rules for enrolling a patient at the current dose level and at a de-escalated dose level, or if the study is suspended to accrual. There will be no intra-patient dose escalation.

Table 6-1. Decision Rules for Patient Enrollment Using the Rolling Six Design

Number of Patients Enrolled	Number of Patients with DLT	Number of Patients without DLT	Number of Patients with Data Pending	Decision
2	0 or 1	0, 1, or 2	0, 1, or 2	Same dose level
2	2	0	0	De-escalate[1]
3	0	0, 1, 2, or 3	1, 2, or 3	Same dose level
3	1	0, 1, or 2	0, 1, or 2	Same dose level
3	≥ 2	0 or 1	0 or 1	De-escalate[1]
4	0	0, 1, 2, 3, or 4	1, 2, 3, or 4	Same dose level
4	1	0, 1, 2, or 3	0, 1, 2, or 3	Same dose level
4	≥ 2	0, 1, or 2	0, 1, or 2	De-escalate[1]
5	0	0, 1, 2, 3, 4, or 5	1, 2, 3, 4, or 5	Same dose level
5	1	0, 1, 2, 3, or 4	0, 1, 2, 3, or 4	Same dose level
5	≥ 2	0, 1, 2, or 3	0, 1, 2, or 3	De-escalate[1]
6	0	0, 1, 2, 3, 4, or 5	2, 3, 4, 5, or 6	Suspend accrual
6	1	1, 2, 3, 4, or 5	0, 1, 2, 3, 4or 5	Suspend accrual
6	≥ 2	0, 1, 2, 3, or 4	0, 1, 2, 3, or 4	De-escalate[1]

DLT = dose-limiting toxicity; MTD = maximum-tolerated dose

[1] If 6 patients already entered at the next lower dose level, the MTD has been defined.

Using the rolling 6 design, the determination of DLT and the MTD and/or RP2D will be based on entinostat in combination with avelumab in Cycles 1 and 2. Six patients must be treated at a dose level before it is considered the MTD or RP2D. Patients will receive entinostat orally at the assigned dose on Days 1 and 8 along with avelumab 10 mg/kg mg on Day 1 of a 14-day cycle. Dose group 1 will receive 5 mg entinostat weekly. If the entinostat 5-mg dose exceeds the MTD, then a 3-mg dose of entinostat (Dose Group -1) will be evaluated. If the entinostat 3-mg dose exceeds the MTD, then a 2-mg dose of entinostat (Dose Group -2) will be evaluated. No dose escalations are planned.

Six patients must be treated at a dose level before it is considered the MTD or RP2D. If < 33% of patients within a cohort have a DLT (i.e., <2 of 6), 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 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 Cycles 1 and 2, 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 Phase:

In the Expansion Phase, the efficacy and safety of entinostat (compared to placebo) in combination with avelumab will be evaluated using the RP2D determined appropriate for combination with avelumab in the Dose Determination Phase. Up to 120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab plus entinostat or avelumab plus placebo in a 2:1 ratio, respectively. The randomization will be stratified by the presence of bulky disease (defined as a tumor ≥50 mm) versus not and by a history of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not.

An initial safety evaluation will be performed by a DSMB based on the first 20 patients who are randomized and receive at least 1 administration of study treatment. The safety evaluation will be held after the first 20 patients have completed at least 4 weeks of follow-up after the initiation of study treatment or terminated therapy earlier due to toxicity. Enrollment may continue while the DSMB conducts their initial review. The assessment of the DSMB for this and subsequent safety reviews will focus on deaths (due to any cause), treatment modifications, treatment discontinuations, and serious adverse events. Any adverse safety signals will be assessed by the

committee based on the committee's collective clinical experience rather than on prospective statistically-based early stopping rules. Depending on the outcome of the review, the DSMB may recommend continuation, termination, or modification of the study, as appropriate.

The DSMB also will be responsible for reviewing the results of selected efficacy data once 65 PFS failures (67% of total events) occur, which is anticipated to occur approximately 14 months after the first patient is enrolled in the expansion phase of the study. Given the early stage of development, preliminary anti-tumor activity of the investigational treatments may be evaluated by the DSMB periodically prior to the planned interim analysis to supplement the aforementioned safety reviews.

6.2 Number of Centers

Up to approximately 30 study centers in the US are planned to participate in this study. Study centers that do not enroll at least one patient within 3 months of study center initiation may be subject to closure in consultation with the Sponsor.

6.3 Number of Patients

Up to 138 patients are anticipated if the study completes all phases of evaluation (up to 18 patients for Phase 1b; up to 120 patients for Phase 2).

Phase 1b/Safety Lead-in (Dose Determination Phase):

Up to 18 patients are expected to be enrolled in the Dose Determination Phase of the study, which will employ a rolling 6 phase 1 trial design. Six patients must be treated at a dose level for it to be considered MTD or the RP2D. Each patient will be counted in only 1 dose cohort. Entinostat dosing will begin at 5 mg orally (PO) weekly, decrease to 3 mg weekly if the 5-mg weekly dose exceeds the MTD, and will again be de-escalated to 2 mg weekly should the 3-mg weekly dose exceed the MTD. 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 2 will not be evaluable for the primary Safety endpoint and will be replaced.

Phase 2 Expansion Phase

Up to 120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab with entinostat or placebo in a 2:1 allocation. Note: It is anticipated that the number of patients who will drop out of the study without prior PFS failure will be low (expected not to exceed 2% to 3%). Depending on the actual number of such dropouts, the number of patients accrued may be increased by 6 to 12 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; 3 months for the Phase 1b component and 12 months for the Phase 2 component. Patients may continue study treatment until unequivocal PD, intolerable toxicity, or one of the study withdrawal criteria is met (Section 11). Patients will be followed for overall survival until the Sponsor terminates the trial.

7. PATIENT ELIGIBILITY

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for participation in the study.

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. Histologically or cytologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer
3. Recurrent or progressive disease on or after initial platinum-based chemotherapy for the diagnosis in Inclusion Criterion #2
4. Evidence of measureable disease (according to RECIST 1.1) based on imaging studies (e.g., CT, MRI) within 28 days before the first dose of study drug
5. Previously received at least 3, but no more than 6, lines of therapy including at least 1 course of platinum-based therapy
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Has adequate organ and bone marrow function within 21 days before enrollment as defined below:

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
Renal	
Creatinine **OR** Measured or calculated[1] creatinine clearance (CrCl) (glomerular filtration rate 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
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)	≤ 3.0 × ULN

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

8. If a female of childbearing potential, has a negative urine pregnancy test during screening and a negative urine pregnancy test within 3 days prior to enrollment. If the screening pregnancy test is done within 3 days prior to enrollment, a repeat urine test is not required. A serum pregnancy test is required if the urine pregnancy test is positive. Note: Women of childbearing potential are any women between menarche and menopause (including women who have experienced menopause onset < 12 months prior to enrollment) who have not been permanently or surgically sterilized and are capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion.
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 a patient underwent major surgery or radiation therapy of > 30 Gray, she 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. Non-epithelial tumor ovarian carcinomas or ovarian tumors with low malignant potential (i.e., borderline tumors)
2. Another known malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma or cervical intraepithelial neoplasia/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.
3. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
4. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent (See Appendix 4). Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
5. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry and are neurologically stable. Patients with a history of carcinomatous meningitis are not eligible.

6. 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)
7. 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:
    - 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 congestive heart disease (Appendix 2), or a QTc interval >470 msec;
    - Coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism within 6 months prior to screening;
    - History of Torsades de pointes, ventricular tachycardia, or ventricular fibrillation;
    - Uncontrolled hypertension or diabetes mellitus; or
    - Active infection requiring systemic therapy. Uncomplicated and asymptomatic urinary tract infections are allowed with oral antibiotic treatment (IV antibiotics are prohibited).
8. Any contra-indication 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
9. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies)
10. Known active hepatitis B (e.g., hepatitis B surface antigen [HbsAg]-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 [HBcAb] and absence of HbsAg) are eligible. Hepatitis B virus DNA test must be performed in these patients prior to randomization. Patients positive for hepatitis C virus antibody are eligible only if polymerase chain reaction is negative for hepatitis C virus ribonucleic acid (RNA).
11. Allergy to benzamide or inactive components of entinostat
12. History of allergies to any active or inactive ingredients of avelumab and known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI CTCAE v4.03)
13. Previously treated with a histone deacetylase inhibitor (i.e., vorinostat, belinostat, romidepsin, panobinostat), PD-1/PD-L1-blocking antibody (i.e., atezolizumab, nivolumab, pembrolizumab), or a CTLA-4 agent
14. Received a live vaccine within 30 days of the first dose of treatment
15. Received prior anti-cancer mAb or anti-vascular endothelial growth factor (VEGF) within 4 weeks prior to enrollment or has not recovered (i.e., ≤ Grade 1 at enrollment) from adverse events due to mAb agents administered more than 4 weeks earlier

16. Received prior systemic anti-cancer therapy within 4 weeks or 5 half-lives, whichever is shorter, targeted small molecule therapy or radiation therapy within 2 weeks prior to enrollment, or has not recovered (i.e., ≤ Grade 1 at enrollment) from adverse events 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.

17. Currently receiving treatment with any other agent listed on the prohibited medication list (Section 9.12)
18. Currently enrolled in (or completed) another investigational drug study within 30 days prior to study drug administration
19. Is pregnant, breastfeeding, or expecting to conceive starting with the screening visit through 120 days after the last dose of study drug
20. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

8. PATIENT ENROLLMENT

Section 14.3 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.

After a patient has been screened and successfully fulfills all eligibility criteria, a site representative will enter the patient's assigned study number, eligibility information, and disease status for stratification (bulky disease defined as presence of a tumor ≥50 mm versus not) and by a history of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not, in the electronic data capture (EDC) system. Once the information has been reviewed and approved by Syndax within the EDC system, the patient will officially be enrolled. This patient identification (ID) number must be used on all study documentation related to that patient. In the Phase 2 portion of the study, patients will be randomized to 1 of the blinded study arms within EDC. Refer to the Study Manual for details on the enrollment and randomization procedures, screen failures, and exemption requests.

9. TREATMENT PROCEDURES

9.1 Study Drug

The study drugs being studied in combination during this clinical trial are entinostat and avelumab. The first dose of study treatment is to be administered within 3 days of enrollment 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 film-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, up to 25°C (77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F), in a secure, locked storage area to which access is limited.

The pharmacist will dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers. Entinostat and placebo will be supplied in bottles containing 40 tablets; the pharmacist will dispense product to patients from these bottles.

In the Phase 1b portion of the study, the pharmacist will dispense enough drug for one cycle of treatment, with no additional doses.

During the Phase 2 portion of the study, the unblinded pharmacists will check the EDC/IVR system for patients' randomization codes and repackage entinostat or placebo tablets according to the assignment. The pharmacist will dispense enough tablets of entinostat/placebo for 1 cycle of treatment, plus 1 additional dose (e.g. 3 tablets of 5 mg active / placebo for 5 mg doses or 9 tablets active / placebo for 3 mg doses). The additional tablets are provided in case tablets are lost. The bottles for the Phase 2 portion of the study should be labeled in a randomized fashion to maintain treatment blinding.

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

9.2.2 Dosing and Administration

All patients will self-administer entinostat/placebo orally once weekly on study Days 1 and 8 of each 14-day cycle. A new bottle of entinostat/placebo will be dispensed on Day 1 of every2-week cycle, plus an additional dose in case tablets are lost. On study days on which patients receive both entinostat/placebo and avelumab, entinostat/placebo is to be taken prior to avelumab. On study days on which patients are in clinic for a scheduled visit, patients must bring their entinostat/placebo supply to the visit so that they may dose while in the clinic.

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 electronic case report form (eCRF).

If entinostat/placebo is vomited, the dose should not be re-administered but instead should be skipped. The medical monitor may be consulted should an alternate decision to re-administer entinostat be merited.

9.2.2.1 Phase 1b

During the Phase 1b Dose Determination Phase, all patients will receive avelumab 10 mg/kg as a 1-hour IV infusion every 2 weeks on Day 1 of each 14-day cycle. They will also receive entinostat orally weekly on Days 1 and 8 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 for reasons other than study drug-related toxicity before completing Cycle 2 will be replaced.

9.2.2.2 Phase 2

During the Phase 2 Dose Expansion Phase, all patients will receive avelumab 10 mg/kg as a 1-hour IV infusion every 2 weeks on Day 1 of each 14-day cycle. They will also receive the RP2D of entinostat or matched placebo weekly on Days 1 and 8 of each cycle. Entinostat/ placebo will be administered in a 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 Avelumab

Avelumab is a fully human IgG1 antibody directed against PD-L1 with a calculated molecular weight of 143,832 Dalton. The antibody is produced by mammalian cell culture in a serum-free growth medium, and is purified by affinity, ion-exchange, and mix-mode chromatography. The process also includes specific viral inactivation and removal steps. The antibody is then transferred into formulation buffer and brought to the desired concentration.

9.3.1 Supply and Storage

Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at a concentration of 20 mg/mL in European Pharmacopeia and US Pharmacopeia type I glass vials closed with a rubber stopper and sealed with an aluminum crimp seal closure.

Based on data from ongoing long term stability studies, avelumab drug product must be stored at 2°C to 8°C until use. Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

9.3.2 Dosing and Administration

The dose level of avelumab in this study is 10 mg/kg administered as IV infusion over 1 hour every 2 weeks. For administration in clinical trials, avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. No other drugs should be added to the solution for infusion containing avelumab.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for each dose to ensure they did not experience either a weight loss or gain of >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes to +20 minutes is permitted (i.e., infusion time is 50 to 80 minutes). The exact duration of infusion should be recorded in both source documents and eCRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 9.10.2.2.

The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic

conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user.

Avelumab should be administered in a setting with immediate access to an intensive care unit or equivalent environment allowing for the administration of therapy for anaphylaxis and/or immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

To mitigate avelumab infusion-related reactions, subjects will receive a mandatory premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (per local practice) approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

The mandatory 2-hour observation period after each avelumab infusion (for potential infusion-related reactions) is only required following the first 4 avelumab infusions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued. Patients who experience an infusion-related reaction at any point, must continue to undergo the mandatory observation after each infusion.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration 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 avelumab.

9.4 Study Drug Accountability

The lot numbers of the study drugs (entinostat and avelumab) 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 Treatment Compliance

9.5.1 Entinostat

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.

9.5.2 Avelumab

Avelumab will be administered at the investigational site by appropriately trained study site personnel. Records of treatment administration for each subject will be kept during the study. Clinical research associates will review study drug administration records and verify compliance with the Pharmacy Manual during site visits and at the completion of the study.

9.6 Dose-limiting Toxicity

In the Phase 1b Safety Lead-in (Dose-Determination Phase), DLTs will be assessed during a DLT assessment window, which is the first 28 days from the first dose of both study drugs (from Cycle 1 Day 1 through the end of Cycle 2). The DLT assessment window will apply during the Dose Determination Phase only.

A patient who incurs an adverse event meeting DLT criteria during Cycle 1 or Cycle 2 or who receives the full dose of avelumab and all doses of entinostat during Cycle 1 through the end of Cycle 2 without incurring a DLT, is considered a DLT-evaluable patient.

Patients who withdraw or are withdrawn from either study treatment prior to completing the DLT assessment window for any reason other than a study drug-related toxicity through Cycle 2, will not be considered evaluable for DLTs and will be replaced.

A DLT is defined as the occurrence of any of the following events within the first 2 cycles of treatment (i.e., from Cycle 1 Day 1 through the end of Cycle 2) of entinostat in combination with avelumab that are considered by the Investigator to be at least possibly related to study drug.

- Grade 5 events
- Hematological toxicities
  - Grade ≥4 neutropenia (ANC <500/μL) lasting ≥7 days
  - Grade ≥3 febrile neutropenia
  - Grade ≥4 thrombocytopenia lasting >48 hours
  - Grade ≥3 thrombocytopenia with clinically significant bleeding
  - Grade ≥4 anemia
- Non-hematological toxicities
  - Any grade ≥4 non-hematological toxicity
  - Criteria meeting Hy's law (elevation of ALT/AST ≥3 times ULN and simultaneous total bilirubin ≥2 times ULN)
  - For patients with Grade ≤1 AST, ALT, and/or alkaline phosphatase abnormality at enrollment, an increase to >10 x ULN that does not resolve to Grade ≤ 1 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 ≤ 1 within 72 hours 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 at least 2 doses of entinostat during the first cycle due to toxicity
- If a patient is unable to receive at least 3 doses of entinostat or 60% of the planned entinostat dose, or 2 infusions of avelumab, during the first 2 cycles due to toxicity, this will also be considered a DLT.

All DLTs will be reported in the Sponsor's EDC system within 24 hours. All DLTs will be considered adverse events of special interest for this protocol and will be reported to the Sponsor in an expedited manner. Refer to Adverse Event Reporting Procedures in the Study Manual.

9.7 Maximum Tolerated Dose

The 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 24 months. Patients may remain on study until unequivocal PD, unacceptable toxicity, or another treatment withdrawal criterion is met per Section 11. Patients with evidence of radiological PD who meet the criteria set forth in 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 1 of the 2 study drugs (entinostat/placebo or avelumab), the patient may continue to receive monotherapy for up to 2 years, unless alternate therapy is started or another discontinuation criterion is met (Section 11).

Patients who discontinue both study drugs will receive standard of care outside the auspices of this study at the Investigator's discretion.

After discontinuation of both study drugs, patients will complete an EOT visit within 7 days (± 3 days) after the last dose of study drug and a Safety Follow-up visit 30 days (± 7 days) after the EOT visit. After completion of the 30-day Safety Follow-up visit, patients who have not experienced PD will continue to undergo radiological assessments every 6 weeks until Week 36, and then every 8 weeks thereafter until PD. 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 status until closure of the study or patient death, whichever should occur first.

9.10 Dose Interruptions and Modifications

Although entinostat and avelumab have distinct toxicity profiles, they do share some adverse events such as fatigue and nausea. There is also the possibility that one 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. 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. Note: If a patient permanently discontinues both study drugs (entinostat/placebo and avelumab), the patient will be taken off study treatment.

For avelumab, no dose modifications are permitted, but doses may be omitted based on persisting toxicity. Guidance for entinostat dose interruptions and modifications can be found in Section 9.10.1. All dose modifications should be based on the adverse event 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.

In Phase 1b, dose delays, but not dose reductions will be allowed for entinostat through the end of Cycle 2. If a dose reduction is required during the first two cycles, the patient will be taken

off study. 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 Entinostat Guidelines for Toxicity Management

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 Phase 1b through the end of Cycle 2.

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

Toxicity	Dose modifications
Grade 4	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions. 1. If recovered within 4 weeks of onset (i.e., ≤ 3 missed doses) , resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, discontinue study treatment 2. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions: 1. If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose. 2. If recovered by the 4th dose, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. • If receiving 2 mg, permanently discontinue study treatment. 3. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the **same** Grade 3 toxicity despite dose reduction	If the **same** ≥Grade 3 event **recurs:** 1. Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline. 2. If recovered for either of the next 2 scheduled doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, permanently discontinue study treatment
≤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 Phase 1b through the end of Cycle 2.

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 under the following directions. 1. If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose. 2. If recovered within 2-4 weeks, 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 the 5-mg or 3-mg dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the **same** hematologic toxicity	If the same hematologic toxicity **recurs**: 1. Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline. 2. If recovered for either of the next 2 scheduled doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, permanently discontinue study drug 3. 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 Avelumab Guidelines for Toxicity Management

Because inhibition of PD-L1 stimulates the immune system, avelumab may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (Naidoo 2015; Postow 2015; Weber 2015).

Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related and managed according to guidelines described in Section 9.10.2.4.

For avelumab, no dose modifications are permitted in this study, but doses may be omitted based on persisting toxicity. Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Sponsor approval. The acceptable length of interruption will depend on agreement between the investigator and the Sponsor.

9.10.2.1 Adverse Drug Reactions Requiring Discontinuation or Delay

The following adverse drug reactions (ADRs) require permanent treatment discontinuation of avelumab:

- Any Grade 4 ADRs require permanent treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.
- Any Grade 3 ADRs require permanent treatment discontinuation of avelumab except for any of the following:
  - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management.
  - Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤ 1.
  - Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.
  - Tumor flare phenomena defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- For any Grade 2 ADR, avelumab dosing should be managed as follows:
  - If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
  - If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, the infusion should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the patient should permanently discontinue treatment (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same patient, treatment with avelumab has to be permanently discontinued.

9.10.2.2 Infusion-Related Reactions and Hypersensitivity Reactions

Special Precautions for Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting with immediate access to an intensive care unit or equivalent environment allowing for the administration of therapy for anaphylaxis, and/or immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

To mitigate avelumab infusion-related reactions, subjects will receive a mandatory premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (per local practice) approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. The mandatory 2-hour observation period after each avelumab infusion (for potential infusion-related reactions) is only required following the first 4 avelumab infusions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued. Patients who experience an infusion-related reaction at any point, must continue to undergo the mandatory observation after each infusion. If an allergic reaction occurs, the patient must be treated according to the best available medical practice. The emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Treatment Modifications for Avelumab Infusion-Related Reactions

Treatment modifications for avelumab infusion-related reactions are outlined in Table 9-3.

Table 9-3. Avelumab: Treatment Modifications for Symptoms of Infusion-related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening. The total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Stop the avelumab infusion immediately and disconnect infusion tubing from the patient. Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.
Grade 4: Life-threatening consequences – urgent intervention is indicated.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs

Additional Modifications for Patients with Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 9-3 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next cycle, the investigator may consider the addition of H_2-blocker antihistamines (e.g., famotidine or ranitidine) in addition to the mandatory premedication. However, prophylactic steroids are NOT permitted. If the patient has a second infusion-related reaction of Grade 2 or higher on the slower 50% infusion rate, with or without the addition of further medication to the mandatory premedication, the infusion should be stopped and the patient removed from avelumab treatment. If the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

9.10.2.3 Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms include impaired airway, decreased oxygen saturation (< 92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the intensive-care unit should be alerted for possible transfer if required.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (e.g., paracetamol) may be given to patients at the discretion of the investigator.

9.10.2.4 Immune-related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, immune-related adverse events (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade) as outlined in Table 9-4:

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to high-grade adverse events (Grades 3 to 4).
- Grades 3 to 4: treat with high-dose corticosteroids.

Table 9-4. Avelumab: Management of Immune-related Adverse Events

Gastrointestinal Immune-related Adverse Events		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	Continue avelumab therapy symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms. Educate patient to report worsening immediately. If worsens, treat as Grade 2 or Grade 3 to 4.
Grade 2 Diarrhea: 4 to 6 stools/day over baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy; symptomatic treatment.	If improves to Grade 1, resume avelumab therapy. If persists > 5 to 7 days or recurs, give 0.5 to 1.0 mg/kg/day methyl-prednisolone or equivalent. When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids, treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools/day over baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL. Colitis (Grade 3): severe abdominal pain; medical intervention indicated; peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol; give 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves, continue steroids until Grade 1, then taper over at least 1 month. If persists > 3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contra-indication). Note: Infliximab should not be used in cases of perforation or sepsis.
Dermatological Immune-related Adverse Events		
Grade of Rash (NCI-CTCAE v4.03)	Management	Follow-up
Grades 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids). Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: consider skin biopsy; delay avelumab therapy. Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy. If worsens, treat as Grade 3 to 4.
Grades 3 to 4 Covering >30% body surface area; life-threatening consequences	Delay or discontinue avelumab therapy; consider skin biopsy dermatology consult; give 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or IV equivalent	If improves to Grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. Resume avelumab therapy.

Table 9-4. Avelumab: Management of Immune-related Adverse Events

Pulmonary Immune-related Adverse Events		
Grade of pneumonitis (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 Radiographic changes only	Consider delay of avelumab therapy; monitor for symptoms every 2 to 3 days; consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks. If worsens, treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy; Pulmonary and Infectious Disease consults; monitor symptoms daily, consider hospitalization; give 1.0 mg/kg/day methylprednisolone IV or oral equivalent; consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days. If improves, when symptoms return to near baseline, taper steroids over at least 1 month, then resume avelumab therapy and consider prophylactic antibiotics. If not improving after 2 weeks or worsening, treat as Grade 3 to 4.
Grades 3 to 4 Severe new symptoms; New or worsening hypoxia; life-threatening	Discontinue avelumab therapy; hospitalize; Pulmonary and Infectious Disease consults; give 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections; consider bronchoscopy, lung biopsy.	If improves to baseline, taper steroids over at least 6 weeks. If not improving after 48 hours or worsening, add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic Immune-related Adverse Events		
Grade of liver test elevation (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3.0 x ULN and/or total bilirubin >ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring. If worsens, treat as Grades 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Delay avelumab therapy; increase frequency of monitoring to every 3 days	If returns to baseline, resume routine monitoring; resume avelumab therapy. If elevations persist > 5 to 7 days or worsen, give 0.5 to 1 mg/kg/day methyl-prednisolone or oral equivalent. When LFT returns to Grade 1 or baseline, taper steroids over at least 1 month. Consider prophylactic antibiotics for opportunistic infections, and resume avelumab.
Grades 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Discontinue avelumab therapy; increase frequency of monitoring to every 1 to 2 days. Give 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade 2, taper steroids over at least 1 month. If does not improve in > 3 to 5 days, worsens or rebounds, add mycophenolate mofetil 1 g twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Table 9-4. Avelumab: Management of Immune-related Adverse Events

Endocrine Immune-related Adverse Event		
Endocrine Disorder	Management	Follow-up
Asymptomatic TSH abnormality	Continue avelumab therapy. If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements, include T4 at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy	Evaluate endocrine function. Consider pituitary scan. If symptomatic with abnormal lab/pituitary scan, delay avelumab therapy; give 1 to 2 mg/kg/day methyl-prednisolone IV or oral equivalent. Initiate appropriate hormone therapy. If no abnormal lab/pituitary MRI scan but symptoms persist, repeat labs in 1 to 3 weeks/MRI in 1 month	If improves (with or without hormone replacement), taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections. Resume avelumab therapy. Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy; rule out sepsis. Stress dose of IV steroids with mineralocorticoid activity; give IV fluids. Consult endocrinologist. If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	
Cardiac Immune-related Adverse Events		
Myocarditis	Management	Follow-up
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab and entinostat therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab and entinostat therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab and entinostat. Guideline based supportive treatment as appropriate per cardiology consult. * Methylprednisolone 1-2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressant (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CT=computed tomography; IV=intravenous; LFT=liver function test; LLN=lower limit of normal; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=non-steroidal anti-inflammatory drugs; T4= thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; CK-MB=creatinine kinase MB isoenzyme; BNP=B-type natriuretic peptide;		

9.11 Concomitant Therapy

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 anti-emetics, with the exception of those listed in Section 9.12. All concomitant treatments and therapies, or medication, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids, administered from 30 days preceding the screening study visit through 90 days after the last dose of study drug must be reported in the 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.

9.11.1 Premedication

Patients will receive a mandatory premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (per local practice) approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

9.11.2 Palliative and Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines. Please refer to Section 9.12 for prohibited medications.

9.11.3 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 4 weeks (2 cycles) of treatment in the Phase 1b Dose Determination Phase, but they may be used at any time to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines. In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines.

9.11.4 Steroid Use

Systemic corticosteroids and anti–tumor necrosis factor (TNF)-α agents may counteract the intended benefit of the proposed study treatment. If feasible, alternatives to these agents should be considered. The use of steroids during this trial is restricted to the following:

- Therapeutic use: For the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 9-4, *Avelumab Management of Immune-related Adverse Events*. The use of systemic corticosteroids to treat disease-related complications or co-morbid medical conditions is strongly discouraged. In consultation with the Sponsor, systemic corticosteroids may be administered, at doses ≤ 10 mg prednisone or for no longer than 7 consecutive days if at higher doses, as clinically indicated, to treat acute conditions, (e.g., exacerbations of chronic obstructive pulmonary disease, pleural effusions, etc.) other than immune-mediated toxicity related to study drug.
- Physiologic use: The use of physiologic doses of corticosteroids for prolonged periods may be approved in consultation with the Sponsor. The use of inhaled steroids for the management of asthma or the use of prophylactic corticosteroids to avoid allergic reactions is permitted. 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. Patients may receive other medications that the Investigator deems to be medically necessary.
- Prophylactic use, e.g., for the prevention of acute infusion-related reactions is prohibited.

9.11.5 Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the study. 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). 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 Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician.

There are no prohibited therapies during the Safety Follow-up period.

9.12 Prohibited Medications and Medications to be Avoided During the Study

The exclusion criteria (Section 7.2) describe medications that are prohibited during the study.

9.12.1 Prohibited Medications

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

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy other than avelumab
- Investigational agents other than entinostat and avelumab
- Prophylactic use of hematopoietic colony stimulating factors are not allowed during the first two cycles of the Phase 1b Dose Determination Phase, but can be used to treat hematological adverse events and for prophylaxis subsequently, per investigator discretion during the Expansion Phase.
- Radiation therapy: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille de Calmette et Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- The use of systemic corticosteroids to treat disease-related complications or co-morbid medical conditions is strongly discouraged. In consultation with the Sponsor, systemic corticosteroids may be administered, at doses no greater than 10 mg prednisone or for no longer than 7 consecutive days if at higher doses, as clinically indicated, to treat acute conditions, (e.g. exacerbations of chronic obstructive pulmonary disease, pleural effusions, etc.) other than immune-mediated toxicity related to study drug. The corticosteroid regimens used to treat the immune-related toxicity related to study drug are specified in Table 9-4, *Avelumab Management of Immune-related Adverse Events*.
- The use of physiologic doses of corticosteroids for prolonged periods may be approved in consultation with the sponsor. The use of inhaled steroids for the management of asthma or the use of prophylactic corticosteroids to avoid allergic reactions is permitted.

- 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.
- Receptor activator of nuclear factor-κB ligand (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 interleukin (IL)-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with avelumab. Patients should not receive other immunomodulatory agents for 10 weeks after the last dose of avelumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of avelumab.
- Use of steroids to premedicate patients for whom CT scans with contrast are contra-indicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the abdomen and pelvis with a non-contrast CT scan of the chest must be performed

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.

9.12.2 Medications to be Avoided During the Study

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

- Gastric acid reducing drugs (e.g. proton pump inhibitors, histamine receptor antagonists [H2], antacids; see Appendix 3)
- Sensitive substrates of cytochrome P (CYP)1A2, CYP2C6, and CYP2B8 (see Appendix 3)
- Drugs that are known to inhibit or induce permeability glycoprotein (P-gp) (see Appendix 3)

Should the use of these medications be required, Syndax must be consulted for guidance. Patients will be allowed to take gastric acid reducing drugs if they agree to hold administration for 3 days prior to each entinostat dose.

9.13 Diet/Activity/Other Considerations

9.13.1 Diet

Entinostat is to be taken on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal. Patients should otherwise maintain a normal diet unless modifications are required to manage an adverse event such as diarrhea, nausea, or vomiting.

9.13.2 Contraception

Patients of childbearing potential should be informed that taking either of the study drugs may involve unknown risks to the fetus (unborn baby) if a pregnancy were to occur during the study. Specifically, the study drugs may have adverse effects on a fetus in utero. To participate in the study, patients with reproductive potential must adhere to contraception methods that result in a failure rate of < 1% per year (described below) from the first screening visit throughout the study period during the treatment period and for at least 120 days after the last dose of study treatment (as defined in Section 7.1). 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.

A woman is considered to be of childbearing potential if she has experienced menarche and is not yet post-menopausal and has not been permanently or surgically sterilized. A woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered post-menopausal. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but not does include bilateral tubal occlusion.

Patients with reproductive potential must agree to use acceptable contraceptive methods with a <1% annual failure rate or to remain abstinent (refrain from heterosexual intercourse). The following are acceptable methods of contraception:

Single method (one of the following is acceptable):

- intrauterine device
- bilateral tubal ligation
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection)

Either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy would be considered acceptable.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by the local regulatory agencies and Ethics Committee (EC)/Institutional Review Board (IRB). Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

As discussed above, these contraceptive methods must be used for 120 days after the last dose of study drug. Patients must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period to participate in the study. 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.

9.13.3 Study Drug Use in Pregnancy

If a patient 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 the Sponsor 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.

9.13.4 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 within 3 days of the date of enrollment.

A cycle is 14 days in length. During treatment, patients will attend study center visits for study evaluations on Days 1 and 8 of Cycles 1 and 2; and on Day 1 of each cycle thereafter. Patients will have radiological disease assessments performed within 28 days prior to enrollment, and then every 6 weeks (± 3 days) when measured from Cycle 1 Day 1, through Week 36 (Weeks 6, 12, 18, 24, 30, 36) until unequivocal PD per RECIST 1.1. Patients remaining on study after Week 36 will undergo radiological disease assessments every 8 weeks (± 3 days) until unequivocal PD occurs. Disease will be assessed by CT and MRI, as appropriate using the same method as used for the screening evaluation, and response will be assessed by the Investigator using RECIST 1.1 and irRECIST. This schedule is to be followed both during study treatment and following discontinuation of study treatment in the absence of PD.

Patients will remain on study treatment until unequivocal PD, intolerable toxicity, or one of the other study withdrawal criteria is met, or closure of the study by the Sponsor (Section 11). Patients with radiographic progression only, as defined by RECIST 1.1 should continue on study treatment until unequivocal PD is determined as defined by irRECIST, at the discretion of the Investigator. After study treatment discontinuation, patients will complete an EOT visit within 7 days after the last dose of study drug and 3 Safety Follow-up visits 30, 60, and 90 days (± 7 days) after the EOT visit. The 60-day Safety Follow-up will be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care). The 90-day visit may also be conducted via telephone in the absence of an ongoing toxicity requiring an office assessment (per Investigator's judgement and standard of care) given that the patient's 90-day thyroid function tests are assessed locally. Patients with ongoing toxicities will be followed more frequently per the Investigator's clinical judgement and standard of care. For example, Grade 3 or higher laboratory toxicities will be assessed at least

weekly until resolution to Grade 2 or baseline grade. Entinostat and avelumab related toxicities will be managed as outlined in Section 9.10.1.

After completion of the 30-day (± 7 days) Safety Follow-up visit, patients who have not experienced PD are to be followed every 6 weeks for a clinic visit and radiological imaging until unequivocal PD or until Week 36, whichever occurs first. If PD has not been documented at Week 36, patients will be followed every 8 weeks for radiological imaging until unequivocal PD, death, or end of the study, whichever occurs first. Following documentation of PD, patients will be contacted every 3 months to document survival status and post-study therapies until death or closure of the study by the Sponsor.

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 will include cancer history, including date of and stage at diagnosis, method of diagnosis, 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 urine pregnancy test is to be performed during screening and within 3 days before the first study drug dose if the screening pregnancy test is performed

more than 3 days before the first study drug dose. If the urine pregnancy test is positive, a serum blood pregnancy test must be performed. Results must be available and confirmed to be negative prior to enrollment. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

10.2 Safety Assessments

10.2.1 Vital Signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiration rate (breaths per minute), and temperature, are to be measured during screening, on Day 1 of each treatment cycle, at the EOT visit (7 days post-last dose) and the Safety Follow-up visits.

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.

10.2.2 Weight

Weight is to be measured during screening, on Day 1 of each treatment cycle, at the EOT visit and the Safety Follow-up visits.

10.2.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status is to be assessed during screening, on Day 1 of each treatment cycle, and at the EOT and Safety Follow-up 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		Karnofsky	
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

ECOG = Eastern Cooperative Oncology Group
References: Oken 1982; Mor 1984

10.2.4 Adverse Events

Adverse events, as defined in Section 12.2.1, are to be documented from the time informed consent is signed through 90 days following the last dose, or 30 days after the initiation of a new anticancer therapy, whichever is earlier. However, events meeting the definition of serious or an adverse event of special interest (AESI) that occur after signing the informed consent form but before the first study drug dose, are to be reported as described in Section 12.4 and Section 12.4.3.

10.2.5 Physical Examination

A complete physical examination will be conducted for all patients during screening; enrollment; the EOT visit (within 7 days post-last dose); and at the Safety follow-up visits. If the screening

complete physical examination was performed within 7 days of enrollment, then a symptom-directed physical examination may be performed prior to enrollment. The complete physical examination will consist of a minimum evaluation of head, ears, eyes, nose and throat (HEENT), dermatological, respiratory, cardiovascular, gastrointestinal, neurological, and lymphatic, and musculoskeletal systems.

Symptom-directed physical examinations will be performed for all patients on Days 1 and 8 of Cycle 1; Days 1 and 8 of Cycle 2; and on Day 1 of each subsequent cycle.

10.2.6 Electrocardiograms

All patients will undergo a 12-lead electrocardiogram (ECG) during screening, pre-dose on Cycle 7 Day 1, every 6 cycles (12 weeks) thereafter, and again at the EOT visit (within 7 days post-last dose). An ECG may be repeated anytime, as clinically indicated.

Electrocardiograms will be recorded after the patient has rested in a supine position for at least 10 minutes. The Investigator or designated physician will review the paper copies of each 12-lead ECG.

10.2.7 Clinical Laboratory Tests

Blood samples for hematology and clinical chemistries are to be collected during screening, on Days 1 and 8 of Cycle 1; on Days 1 and 8 of Cycle 2; on Day 1 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 Cycle 1 Day 1 unless clinically indicated.

The following analytes are to be measured:

Hematology	
White blood cell count (WBC) with differential	Hemoglobin
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	
Phosphorus	Total protein
	Magnesium (screening only, unless clinically indicated)
Thyroid stimulating hormone (TSH)	
Adrenocorticotropic hormone (ACTH; screening only)	
Thyroxine (T4)	

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 adverse events.

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 PD 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 PD 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 performed prior to initiating the subsequent cycle to rule out PD 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 enrollment. 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 enrollment and may 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 PD. If PD has not occurred by Week 36, radiological assessments will then be done every 8 weeks (± 3 days) until PD. If a patient withdraws from the study for reasons other than PD, radiological assessments will continue on this same study schedule until PD is unequivocally documented. Images should be performed according 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 radiologist 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 enrollment, 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 > 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 14 mm in short axis
- Leptomeningeal disease
- Ascites, pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Abdominal mases or organomegaly identified by physical examination 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 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 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 contra-indicated 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 Cycle 2 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 PD. If PD has not occurred by Week 36, radiological assessments will be then be done every 8 weeks (± 3 days) until unequivocal PD. 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.

For subjects who discontinue study therapy without documented unequivocal PD, every effort should be made to continue monitoring their disease status by tumor imaging every 8 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. Scans from patients who were determined by the Investigator to have a response to treatment (CR or PR) may be reviewed by the core radiologic laboratory to confirm response. 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 will be utilized to account for the unique tumor response characteristics seen with avelumab treatment. Immunotherapeutic agents such as avelumab 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 radiographic progression only as defined by RECIST 1.1, should continue on study treatment until unequivocal PD is determined as defined by irRECIST, at the discretion of the investigator. Therefore, the following process for assessing radiological PD will be used in this study:

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, 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. Specifically, it is recommended that patients continue to receive both avelumab and entinostat 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; and
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Per irRECIST (Appendix 1), if repeat imaging shows < 20% total tumor burden increase compared to nadir, and new lesions (previously identified as basis for initial PD) are stable or improved, and non-target disease (if identified as cause for initial PD) is stable or improved, then PD by irRECIST will not have been confirmed and treatment may be continued.

If repeat imaging confirms PD due to any of the following scenarios, patients will be discontinued from study treatment:

- Total measurable tumor burden remains ≥20% and ≥5 mm absolute increase compared to nadir;
- Non-target disease resulting in initial PD is worse (qualitative);
- New lesion resulting in initial PD is worse (qualitative); or
- Additional new lesion(s) since last evaluation.

Table 10-2. Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of progressive disease	Repeat imaging at next scheduled time point to confirm progressive disease	May continue study drug at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at next scheduled time point to confirm progressive disease per physician discretion only	Discontinue treatment
Repeat scan confirms progressive disease	No additional imaging required	Discontinue treatment	No additional imaging required	Not applicable
Repeat scan shows stable disease, partial response, or complete response	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 patient has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating PD), but the patient 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 Sponsor. 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 discontinue study treatment.

10.4 [redacted]

10.4.1 Blood

[redacted]

10.4.2 Tumor Tissue

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

- Availability of a recent FFPE tumor tissue block from a de novo tumor biopsy during screening. If patients whose only accessible lesion for biopsy is a solitary target lesion, it must be amenable to a core biopsy that will not compromise assessment of tumor measurements. Alternatively, a recently obtained archival FFPE tumor tissue block (cut slides not acceptable) from a primary or metastatic tumor resection or biopsy can be provided if the biopsy or resection was performed within 1 year of randomization or if biopsy is clinically contra-indicated. Availability of an archival FFPE tumor tissue from primary tumor resection specimen (if not provided per above). If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.
- On Cycle 4 Day 1 (+ 3 days) on an optional basis from patients in the Safety Lead-in. All patients will be encouraged to provide an optional biopsy to help understand dose-immune correlate effects.

- On Cycle 4 Day 1 (+ 3 days) on an optional basis for patients in the Phase 2 portion who consent to biopsy
- 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, tumor tissue samples may be collected on a mandatory basis from all subsequent patients on Cycle 4 Day 1 (+ 3 days).

Tissue samples will be sent to a central laboratory facility for preparation and distribution to other central laboratories for analysis. [redacted]

Whole exome sequencing and RNAseq techniques are used to provide a comprehensive analysis of which genes are expressed and at the level at which they are expressed in cancer cells. Nanostring technology provides analysis of expression of panels of pre-specified genes of interest, usually around 600-700 genes. Whole exome sequencing and RNAseq do not pre-specify gene of interest but rather provide the opportunity to examine expression of all genes. All three technologies – Nanostring, whole exome sequencing, and RNAseq can be applied to understand changes in gene expression before and after treatment with either avelumab or the combination of avelumab and entinostat. These changes may help us understand how the treatments are working.

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 pre-dose on Cycle 1 Day 1 and 2 to 4 hours post-dose; anytime post-dose on Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 4 Day 1, and pre-dose on Cycle 2 Day 8. These samples will be collected in both the Phase 1b and Phase 2 portions of the study. On each sample collection day, the time and date of entinostat administration, the start and stop time of avelumab 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 Avelumab

Blood samples for determination of avelumab levels and avelumab ADASs will be collected pre-dose and immediately prior to the end of infusion (PK only) on Day 1 of Cycles 1 through 6, then Cycles 8, 10, 12, 16, 20, 28, 32, 36, 48, EOT, and at 30-day Follow-up. Sample must be drawn within 2 hours prior to the start of avelumab infusion, but before any drug (i.e. entinostat) is given. These samples will be collected in both the Phase 1b and Phase 2 portions of the study. Samples should be taken from the arm contralateral to the infusion. On each sample collection day, the time and date of entinostat administration, the start and stop time of avelumab 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.

11. DISCONTINUATION AND REPLACEMENT OF PATIENTS

Patients have the right to withdraw partially or fully 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 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). 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. 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/Safety Lead-in (Dose Determination Phase), patients who discontinue the study for reasons other than study drug-related toxicity before completing Cycle 2 will 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 Phase 2, the number of patients enrolled may be increased by 6 to 12 additional patients to accommodate for a higher than expected number of dropouts without prior documented PD by RECIST 1.1.

12. ADVERSE EVENTS, DATA REPORTING, AND RECORDING

12.1 Study Drugs

12.1.1 Entinostat

Commonly encountered adverse events observed in 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 occurring at a ≥10% higher incidence in entinostat-treated patients versus placebo-treated patients, respectively, included fatigue (48%, 26%), nausea (40%, 15%), neutropenia (30%, 0%), peripheral edema and vomiting (both 21%, 5%), thrombocytopenia (19%, 6%), pain (16%, 6%), and dyspepsia and leukopenia (both 14%, 3%). The only Grade 3 or 4 adverse event occurring at a >10% incidence for subjects receiving entinostat versus those receiving placebo was neutropenia (14% vs 0%). In a Phase 2, randomized, placebo-controlled study in patients with lung cancer, in which patients received erlotinib + entinostat or erlotinib + placebo, treatment-emergent adverse events (defined as adverse events that start on or after the first administration of study drug) reported at a ≥ 10% higher incidence in entinostat-treated patients versus placebo-treated patients, respectively, included nausea (49%, 25%); anorexia (40%, 16%); weight decreased (32%, 18%); dyspnea (31%, 18%); vomiting (31%, 13%); peripheral edema (28%, 13%); anemia (22%, 11%); thrombocytopenia (15%, 3%); hypotension (14%, 2%); and stomatitis (12%, 2%). In a Phase 2 study in patients with metastatic melanoma treated with entinostat monotherapy, the most frequently reported treatment-emergent adverse events 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 avelumab.

12.1.2 Avelumab

Please refer to the current Informed Consent and the Avelumab IB for the current safety profile and information regarding avelumab.

12.2 Adverse Event Definitions

12.2.1 Adverse Events

An adverse event is defined in the ICH Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that 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 adverse event 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 adverse events.

Progressive disease should not be recorded as an adverse event. If PD occurs, record the date first documented in the EOT visit eCRF. Signs and symptoms related to PD should be reported in the appropriate eCRF as an adverse event or as a serious adverse event if the event in question meets the criteria for seriousness. 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. Adverse events ongoing at the end of the study or at the time of death are to be noted as "continuing." Classification of adverse events 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 clinically significant change from baseline.

In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

12.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any adverse event 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 adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

12.2.3 Unexpected Adverse Event

An unexpected adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in Section 6.3 of the entinostat IB (Reference Safety Information) or is not listed at the specificity or severity that has been observed.

12.2.4 Serious Adverse Events

An adverse event 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 an important medical event that although may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay (≥ 24 hours) in a health care facility. Any adverse event 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 "important medical events" criterion for classification as a serious adverse event.

12.3 Reporting Procedures for All Adverse Events

The Investigator is responsible for ensuring that all adverse events (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 eCRF.

The following adverse event attributes must be assigned by the Investigator: event description (with detail appropriate to the event); seriousness; dates of onset and resolution; severity; assessment of relationship to entinostat and to avelumab; 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 entinostat or avelumab or the combination of entinostat with avelumab?" The causal relationship between an adverse event and the study drugs 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 drug(s)
- **Possibly related**: Event may be explained by administration of the study drug(s), 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 patient's clinical state or other agents/therapies

When assessing the relationship between administration of the study drugs and the adverse event, 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 adverse event (U.S. Department of Health and Human Services 2010). For adverse events 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 adverse event is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw consent from treatment due to what she perceives as an intolerable adverse event. 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

Serious adverse events 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 avelumab or the combination. All serious adverse events must be reported to Syndax or its representative within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and provided to Syndax or its representative. The serious adverse event 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 a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the EOT eCRF.

The Investigator should notify the IRB or EC of serious adverse events occurring at the site and other adverse event 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 adverse events, 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 drugs or 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 serious adverse events (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 dose > 10 mg/kg for avelumab and > 15 mg for entinostat. No specific information is available on the treatment of overdose of avelumab or entinostat. The overdose will not be considered a serious adverse event unless the outcome of the overdose meets seriousness criteria as defined in Section 12.2.4. In the event of an overdose, the Sponsor should be immediately notified. The subject should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

12.4.3 Adverse Events of Special Interest with Avelumab

Any adverse event or serious adverse event that is suspected to be a potential immune-related adverse event is considered an AESI. Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune mediated reactions including myositis and myocarditis. Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune related and managed according to guidelines provided in Table 9-4 *Avelumab Management of Immune-related Adverse Events*. Adverse events of special interest are reported according to the general serious adverse event reporting rules specified in Section 12.4.

Toxicities associated or possibly associated with avelumab 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 avelumab 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 avelumab. Avelumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

Any adverse event or serious adverse event that is suspected to be a potential infusion-related adverse event is considered an AESI. Specific guidance for the management of infusion-related adverse events is provided in Table 9-3, *Avelumab: Treatment Modifications for Symptoms of Infusion-related Reactions*. Adverse events of special interest are reported according to the general serious adverse event reporting rules specified in Section 12.4.

For the management of other adverse events associated with the avelumab, refer to the avelumab 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.

For the purpose of this clinical trial, the following adverse events will be considered adverse events of special interest defined by the Sponsor:

- Infusion-related reactions including hypersensitivity reactions
- Immune-mediated adverse reactions such as: immune-mediated colitis; immune-mediated hepatitis including autoimmune hepatitis; immune-mediated thyroid disorders including hyperthyroidism; hypothyroidism; thyroiditis and autoimmune thyroiditis; immune-mediated pneumonitis; immune-mediated skin reactions including rash, pruritus, rash generalized, rash macula-papular, erythema, pemphigoid; other immune mediated reactions including myocarditis, adrenal insufficiency, uveitis, iritis, myositis

12.4.4 Follow-Up of Adverse Events

The Investigator must continue to follow all serious adverse events and non-serious adverse events considered to be definitely, probably, or possibly related to study drug either 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 reasons for such deviations must be noted on the eCRF.

12.5 Period of Observation: Summary

Table 12-2 below summarizes the different observation periods for adverse event, serious adverse event, AESI with avelumab and pregnancy/lactation.

Table 12-2: Adverse Event Observation Periods

Type of Event	Adverse Event	Serious Adverse Event	AESI with Avelumab	Pregnancy/Lactation
Reporting period	From informed consent until 30 days after the end of treatment	From consent until 90 days after the last dose of study treatment for all serious adverse events, and any time after the end of study for serious adverse events believed to be 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 study treatment in case of initiation of a new anticancer therapy. Note: all patients becoming pregnant must be followed to 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

12.6 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 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 DSMB will consist of clinicians and biostatisticians who are experienced in clinical trials of patients with advanced epithelial ovarian cancer and the treatments under investigation. Further details regarding the DSMB will be described in the DSMB Charter.

The safety and tolerability data that will be reviewed by the 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.

The DSMB will review safety data from the Phase 2 portion of the study on a periodic basis, but not less frequently than approximately every 6 months. Unplanned safety review meetings of the DSMB may be called at any time. An initial safety evaluation will be performed by the DSMB based on the first 20 patients who are randomized and receive at least 1 administration of study treatment. The initial safety evaluation will be held after the first 20 patients have completed at least 4 weeks of follow-up after the initiation of study treatment or terminated therapy at an earlier time point due to toxicity. Enrollment may continue while the DSMB conducts their reviews. The assessment of the DSMB for this and subsequent safety reviews will focus on deaths (due to any cause), treatment modifications, treatment discontinuations, laboratory values, adverse events, and serious adverse events. Any adverse safety signals will be assessed by the committee based on the committee's collective clinical experience rather than on prospective statistically-based early stopping rules. Depending on the outcome of the review, the DSMB may recommend continuation, termination, or modification of the study, as appropriate.

The DSMB also will be responsible for reviewing the results of selected efficacy data once 65 PFS failures (67% of total events) occur, which is anticipated approximately 14 months after the first patient is enrolled in the expansion phase of the study. Given the early stage of development, preliminary anti-tumor activity of the investigational treatments may be evaluated by the DSMB periodically prior to the planned interim analysis to supplement the aforementioned safety reviews.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size Estimation

13.1.1 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 rolling 6 phase 1 trial design (Skolnik 2008). Two to 6 patients can be concurrently enrolled into a dose level, dependent upon: (1) the number of patients enrolled at the current dose level; (2) the number of patients who have experienced DLT at the current dose level; and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met.

For example, when 3 participants are enrolled into a dose cohort, if toxicity data are available for all 3 when the 4th participant entered and there are no DLTs, the 4th participant is enrolled. If data are not yet available for 1 or more of the first 3 participants and no DLT has been observed, or if 1 DLT has been observed, the new participant is entered at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants 5 and 6. In place of suspending accrual after every 3 participants, accrual is only suspended when a cohort of 6 is filled. A participant who is inevaluable for toxicity will be replaced with the next available participant if de-escalation rules have not been fulfilled at the time the next available participant is enrolled into the study. Therefore, between 6 and 18 patients will be included in the Phase 1b/Safety Lead-in (Dose Determination) component. Note: patients who discontinue the study for reasons other than study drug-related toxicities before completing Cycle 2 will be replaced.

13.1.2 Phase 2 (Expansion Phase)

The Expansion Phase will evaluate the efficacy and safety of entinostat (compared to placebo) when administered at the recommended Phase 2 dose with avelumab in a randomized, double-blind, placebo-controlled setting. Progression-free survival will be the primary measure of efficacy; secondary measures of efficacy include ORR, CBR, DOR, TTR, and OS. Up to

120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab with entinostat or placebo in a 2:1 allocation. The randomization will be stratified by the presence of bulky disease (defined as presence of a tumor ≥ 50 mm versus not) and by a history of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not.

The sample size was based on the following considerations. The true median PFS for patients with advanced epithelial ovarian cancer receiving avelumab monotherapy is expected to be approximately 3 to 4 months when measured from randomization. It is hypothesized the combination of entinostat and avelumab will reduce the hazard of disease progression or death without documented disease progression beforehand by 43% (i.e., true HR of 0.57). Under the exponential distribution, such a reduction in the hazard rate represents a 75% improvement in true median PFS relative to that of the control arm. If true median PFS is 3 months for patients receiving avelumab monotherapy, then true median PFS will be improved by approximately 2.25 months (i.e., 3 vs 5.25 months). Similarly, if true median PFS is 4 months for the control arm, then true median PFS will be improved by 3.0 months (i.e., 4 vs 7 months).

The primary analysis of PFS will be performed using a stratified log-rank test, stratifying on the randomization stratification factor(s). Total information of 97 PFS failures, defined as documented PD by RECIST 1.1 or death due to any cause without prior documented PD, is estimated to provide 90% power to detect the aforementioned 43% reduction in the PFS failure hazard rate with 1-sided significance level of 0.10 (SEQDESIGN procedure, SAS version 9.2).

Assuming true median PFS is 4 months for the control arm and approximately 12 months of accrual plus an additional 12 months of follow-up, total accrual of 120 patients (80 in the entinostat arm and 40 in the placebo arm) is projected to result in 97 PFS failures within approximately 24 months of the date the first patient is randomized. Patients who discontinue study treatment for reasons not due to documented PD 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 prior PFS failure will be low (expected to not exceed 2% to 3%). Depending on

the actual number of such dropouts, the number of patients accrued may be increased by 6 to 12 additional patients to accommodate for a higher-than-expected number of dropouts.

13.2 Phase 2 Interim Efficacy Analyses

An interim efficacy analysis is planned after 65 PFS failures (67% of total events) occur, which is anticipated to occur approximately 14 months after the first patient is enrolled in the expansion phase. The calendar date of the 65th event will serve as the data cutoff date for the interim analysis. The significance levels at the interim analysis and primary analysis will be adjusted using the O'Brien-Fleming procedure to maintain control of the overall type I error rate for multiple testing (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 are randomized, 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 and 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 avelumab. At least 1 laboratory or other safety-related assessment subsequent to at least 1 dose of entinostat or avelumab 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 who experiences an adverse event meeting DLT criteria during Cycles 1 and 2 or who receives the full dose of avelumab and all doses of entinostat during Cycles 1 and 2 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 Endpoint

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

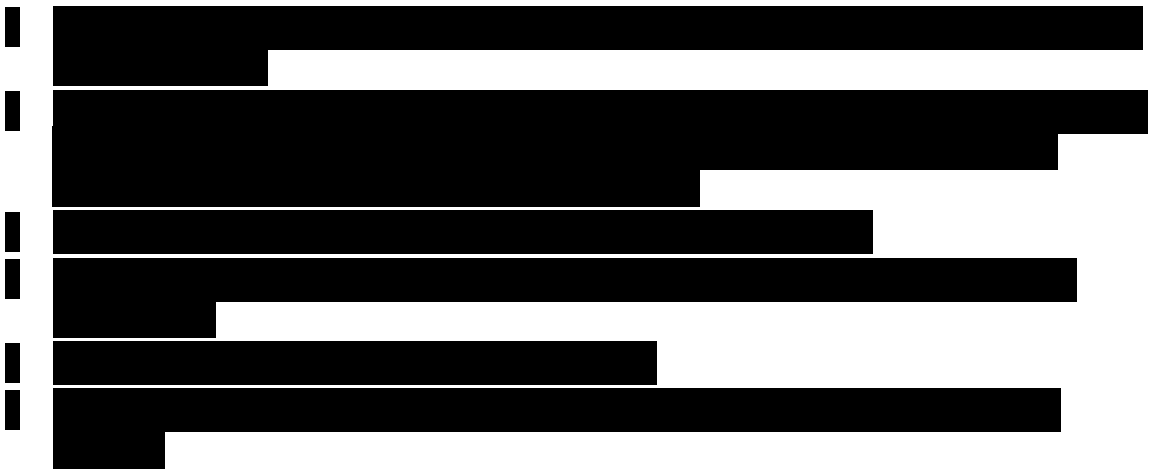
Secondary Endpoints (analyzed using the same populations as the primary endpoint):

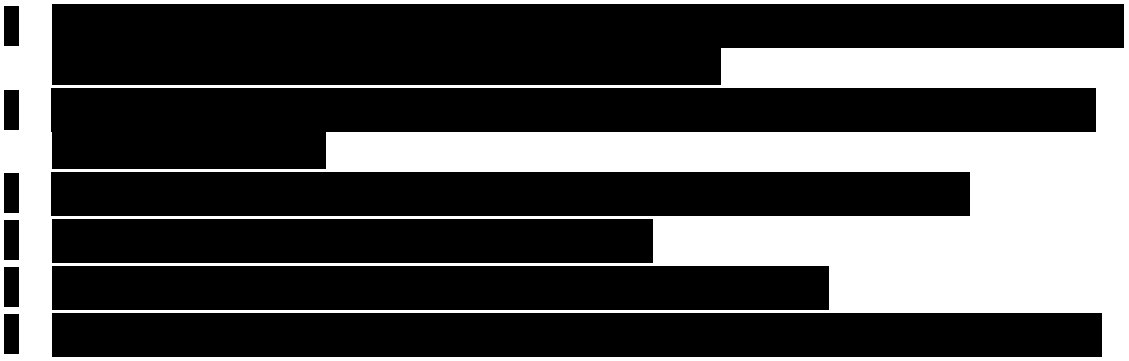
- PFS as determined by irRECIST
- ORR (CR or PR), by RECIST 1.1 and irRECIST
- CBR (CR, PR, or SD for at least 24 weeks) by RECIST 1.1 and irRECIST
- OS
- DOR and TTR (in patients who achieve a best overall response of CR or PR)
- The effect of entinostat on the PK of avelumab

Safety:

- Determination of DLT, MTD, and RP2D
- Incidence of treatment-emergent adverse events, serious adverse events, adverse events resulting in the permanent discontinuation of study drug, and deaths occurring within 30 days of the last dose of study drug
- Change from baseline in vital signs, ECOG, physical examination, ECGs, and laboratory assessments

Exploratory:





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 of both entinostat (in mg) and avelumab (in mg/kg) 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 FAS and, where appropriate, the per-protocol set. The efficacy outcomes for patients enrolled in the Phase 1b portion of the study will be reported in listing format, and may be summarized in a descriptive manner using the analysis conventions described below, as appropriate. The primary analysis of PFS will be based on the first 97 PFS failures, which is anticipated to occur approximately 24 months after the first patient is enrolled in the expansion phase of the study. The calendar date of the 97th event will serve as the data cutoff date for the primary analysis. The primary analysis of the secondary and exploratory endpoints and safety will occur at the time of the primary PFS analysis. An interim efficacy analysis is planned after 65 PFS failures (67% of total events), which is anticipated to occur approximately 14 months after the first patient is enrolled in the expansion phase. The calendar date of the 65th event will serve as the data cutoff date for the interim analysis. 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, 1 month is considered 30.4375 days.

The duration of PFS will be summarized descriptively using the Kaplan-Meier method with 95% CIs 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(s). Estimation of the HR for treatment effect and its corresponding 95% CI will be determined using a stratified Cox proportional hazards model, without any other covariate. Homogeneity in the HRs 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 (US 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).

The association between PFS (and other endpoints) and treatment arm, adjusted for one or more demographic and baseline disease-related characteristics may be explored using multivariate Cox proportional hazards models. Additional supportive analyses may be performed to determine whether the treatment effect that is estimated for the primary analysis is consistent across subgroups of patients based on pertinent demographic and baseline disease-related characteristics. For each subgroup, the hazard ratio for treatment effect will be estimated. Forest

plots may be used to depict the hazard ratio and 95% confidence intervals across subgroups. Kaplan-Meier figures may be provided for each treatment arm within each subgroup. Both multivariate and subgroup analyses will be performed using the FAS. Further details of these analyses will be provided in the Statistical Analysis Plan.

Overall response rate 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. 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 factor(s). The corresponding results without stratification will be reported as supplemental analyses.

Duration of response 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. Duration of response will be summarized descriptively for each treatment arm using the Kaplan-Meier method. Inferential comparisons between treatment arms for DOR are not planned.

Clinical benefit rate 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 6 months. 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.

Overall survival 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. A summary of the anti-cancer therapies and interventions received after the discontinuation of study treatment will be provided.

13.5.6 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including vital signs measurements, ECOG performance status, adverse events, serious adverse events, physical examination findings, ECG results, and laboratory values. Unless specified otherwise, the safety analyses will be conducted for the safety population.

The DSMB will review safety data from the Phase 2 portion of the study on a periodic basis (Section 12.6). An initial safety evaluation will be performed by the DSMB based on the first 20 patients who are randomized and receive at least 1 administration of study treatment. The initial safety evaluation will be held after the first 20 patients have completed at least 4 weeks of follow-up after the initiation of study treatment or terminated therapy at an earlier time point due to toxicity. Enrollment may continue while the DSMB conducts their reviews. The assessment of the DSMB for this and subsequent safety reviews will focus on deaths (due to any cause), treatment modifications, treatment discontinuations, laboratory values, adverse events, and serious adverse events. Any adverse safety signals will be assessed by the committee based on the committee's collective clinical experience rather than on prospective statistically-based early stopping rules. Depending on the outcome of the review, the DSMB may recommend continuation, termination, or modification of the study, as appropriate.

Summary tables and listings will be provided for all reported treatment-emergent adverse events, defined as adverse events that start on or after the first administration of study treatment. The reported adverse event term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse event will be summarized based on the number and percentage of patients experiencing the event by MedDRA system organ class and preferred term. In the event a patient experiences repeat episodes of the same adverse event, 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 treatment-emergent adverse events
- treatment-emergent adverse events by relationship to study treatment and maximum severity grade
- treatment-emergent adverse events with action of study treatment delayed/interrupted or dose reduced
- treatment-emergent adverse events with action of study treatment discontinued
- serious adverse events

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 occurring 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 chemistry laboratory test results 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 CTCAE v 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.

Electrocardiogram 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.

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. Descriptive statistics will be used to summarize the PK of avelumab and anti-avelumab antibodies at each cycle and time point.

Specific details for these analyses as well as analyses of trough avelumab levels and anti-avelumab 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 non-missing data, mean, either the standard error or standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum values will be presented. For discrete data, the frequency and percent distribution will be presented. [redacted] 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 GCP, 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/Ethics Committee

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 serious adverse events occurring at the site and other adverse event reports received from Syndax, in accordance with local procedures.

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 notably:

- Patient files containing informed consent forms and patient identification list
- Study files containing the Protocol with all amendments, IB, copies of pre-study documentation (Section 14.3), 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, 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 Code of Federal Regulations 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

Appendix 1

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 patterns 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). For irRECIST, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1, the irRECIST criteria

- require confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

The irRECIST criteria are defined as follows:

- Overall 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.
- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.
- Overall immune-related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).
- Overall immune-related progressive disease (irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in index, non-index, and new lesions are outlined in Table 17-1.

Table 17-1. Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable Response	Non-measurable Response		
Index and New Measurable Lesions (Tumor Burden)[a]	**Non-Index Lesions**	**New, Non-measurable lesions**	**Overall Response Using irRECIST[b]**
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥ 30%	Absent/stable	Any	irPR
Decrease ≥ 30%	Unequivocal progression	Any	irPR
Decrease < 30% and increase < 20%	Absent/stable	Any	irSD
Decrease < 30% and increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

[a] Decrease assessed relative to baseline.

[b] Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix 2

New York Heart Association 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.

Appendix 3

Concomitant Medications to Avoid

Examples of sensitive *in vivo* CYP substrates and CYP substrates with narrow therapeutic range are summarized in Table 17-2.

Table 17-2: 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 if 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.

Refer to Table 17-3 for examples of transporter inhibitors and inducers.

Table 17-3. 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

Refer to Table 17-4 for examples of gastric acid reducing drugs.

Table 17-4. Gastric Acid Reducing Drugs

Gastric Acid Reducing Drugs[1]	
Proton Pump Inhibitors[2]	• Omeprazole (Prilosec, Zegerid) • Lansoprazole (Prevacid) • Rabeprazole (Aciphex) • Pantoprazole (Protonix) • Esomeprazole (Nexium)
H_2 Inhibitors	• Cimetidine (Tagamet) • Ranitidine (Zantac) • Famotidine (Pepcid) • Nizatidine (Axid)
Antacids	• Alka-Seltzer • Alka-2, Surpass Gum, Titralac, Tums • Milk of Magnesia • Alternagel, Amphojel • Gaviscon, Gelusil, Maalox, Mylanta, Rolaids • Pepto-Bismol

[1] Gastric acid reducing drugs: http://www.everydayhealth.com/ulcer/ulcer-treatment.aspx
[2] Patients will be allowed to take gastric acid reducing drugs if they agree to hold administration for 3 days prior to each entinostat dose.

Appendix 4

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