NCT #NCT02915523

Syndax Pharmaceuticals

STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	adverse event
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
ADaM	Analysis Dataset Model
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to the last measurable concentration
BMI	body mass index
BQL	below the quantifiable limit
BUN	blood urea nitrogen
[redacted]	[redacted]
CBR	clinical benefit rate
CI	confidence interval
C_{max}	maximum plasma concentration
CMO	contract manufacturing organization
CR	complete response
CT	computed tomography
DLT	dose-limiting toxicity

Abbreviation	Full Term
DOR	duration of response
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FAS	Full Analysis Set
HCT	hematocrit
HGB	hemoglobin
HR	hazard ratio
irCR	immune-related complete response
irPR	Immune-related partial response
irRECIST	immune response RECIST
LDH	lactate dehydrogenase
MDSCs	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
NR	no results/not reportable

Abbreviation	Full Term
ORR	overall response rate
OS	overall survival
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
PT	preferred term
PT/INR	prothrombin time or international normalized ratio
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDTM	Study Data Tabulation Model
SOC	system organ class
$t_{1/2}$	elimination half-life
T4	thyroxine
TCR	T cell receptor
TEAE	treatment-emergent adverse event

Abbreviation	Full Term
T_{max}	time at which maximum plasma concentration was observed
TSH	thyroid stimulating hormone
TTR	time to response
WBC	white blood cell
WHO	World Health Organization
λ_z	terminal elimination rate constant

1 INTRODUCTION

Clinical Trial SNDX-275-0603 is a Phase 1b/2 evaluating the combination of entinostat with avelumab in patients with advanced epithelial ovarian cancer. The study consists of 2 phases: an open-label Safety Lead-in (Phase 1b) and an Expansion Phase (Phase 2). The Expansion Phase evaluates the efficacy and safety of entinostat with avelumab, when administered at the recommended Phase 2 dose (RP2D), versus avelumab plus placebo in patients with 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 are randomized in a 2:1 ratio to receive either avelumab plus entinostat or avelumab plus placebo, respectively. The randomization for the Phase 2 portion is to 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.

This SAP contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report for Protocol SNDX-275-0603. The statistical methods and analyses described here are based on those presented in the study protocol.

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

- Phase 1b (Safety lead-in): To determine the dose-limiting toxicities (DLTs) and maximum-tolerated dose (MTD), or RP2D, of entinostat (SNDX-275) given in combination with avelumab
- Phase 2 (Expansion Phase): To evaluate 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 Tumor's version 1.1 (RECIST 1.1).

2.1.2 Secondary Objectives

Efficacy: To evaluate the efficacy of entinostat in combination with avelumab in patients 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, 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 tolerability of entinostat in combination with avelumab, as measured by adverse events (AEs) and clinical laboratory parameters

2.1.3 Exploratory Objectives

[redacted]

2.2 STUDY ENDPOINTS

2.2.1 Primary Efficacy Endpoint

- PFS, as determined by the local investigator according to RECIST 1.1

2.2.2 Secondary Endpoints (analyzed for the same populations as the primary endpoint)

- PFS 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 experience best overall response of CR or PR)
- The effect of entinostat on the PK of avelumab

Safety:

- Determination of DLTs, MTD, and RP2D
- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs resulting in the permanent discontinuation of study drug, and deaths occurring within 30 days of the last dose of study drug
- Changes from baseline in laboratory, vital signs, Eastern Cooperative Oncology Group (ECOG), physical examination, and electrocardiogram (ECG) values

2.2.3 Exploratory Endpoints

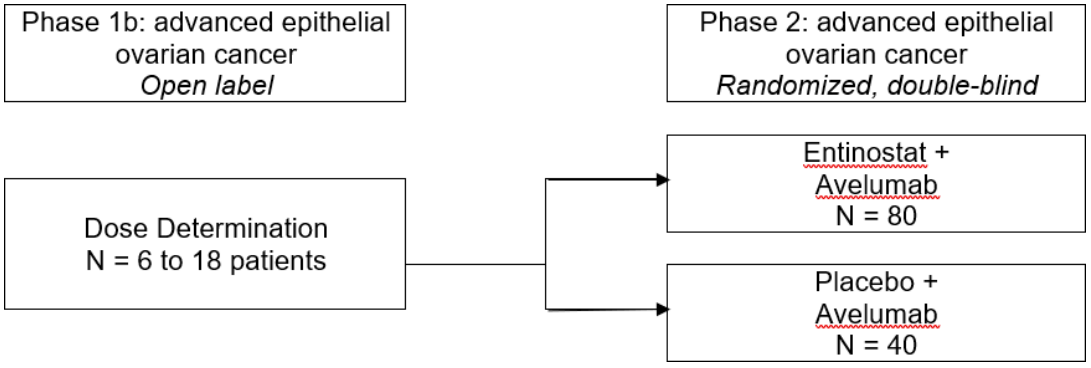
[redacted]

2.3 STUDY DESIGN

Study SNDX-275-0603 is a randomized, placebo-controlled, double-blind, multicenter Phase 1b/2 study evaluating the combination of entinostat with 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 2-1).

A cycle is defined as 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. Collection of fresh tumor tissue core biopsy (image-guided if applicable) and blood samples are outlined in Section 6.1 of the protocol.

Figure 2-1. Study Schema



Patients will remain on study treatment until unequivocal PD, intolerable toxicity, or one of the other study withdrawal criteria is met (see Protocol 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 End of Treatment (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 EOT visit). The 60-day Safety Follow-up will be conducted via telephone in the absence of an ongoing toxicity that requires 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 Protocol Section 9.10.1. The 90-day visit may also be conducted via telephone in the absence of an ongoing toxicity that requires 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 continue to 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.

2.3.1 Number of Patients and Sample Size Considerations

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 unevaluable 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. 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.

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 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.

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 that 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 [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 HR with 1-sided significance level of 0.10 (SEQDESIGN procedure, SAS version 9.4).

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 other than those due to documented PD (per RECIST 1.1) will continue to undergo disease assessments until documented PD, death, withdrawal of consent, or lost to follow-up, whichever occurs first. 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.

An initial safety evaluation will be performed by a Data and Safety Monitoring Board (DSMB) based on the first 20 patients who are randomized and receive at least 1 dose 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 unless therapy is terminated 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 SAEs. 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.

2.3.2 Phase 2 Interim Efficacy Analysis

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).

Based on the projected number of PFS events, the trial will be declared as statistically significant and as having met the primary objective if the observed one-sided p-value is ≤ 0.044 at the interim analysis. If the trial does not reach the O'Brien-Fleming boundary at interim, a final one-sided p-value of ≤ 0.056 is required to be statistically significant at the final analysis of PFS (Table 2-1)

Table 2-1. Properties of the Design for PFS

Information Fraction	Cumulative Events	Cumulative Alpha Spent	Boundary Reject H_0 (1-sided p-value)
0.67	65	0.044	<0.044
1	97	0.1	<0.056

Abbreviation: H_0 = null hypothesis; PFS = progression free survival.

The actual alpha spent and p-value required to reject the null hypothesis will be calculated based on the actual number of events observed at the time of each analysis using software that implements the alpha-spending function noted above (SAS 9.4 or above).

The DSMB will review the unblinded efficacy data during the interim analysis. If the efficacy data meet the pre-specified threshold, the DSMB will be instructed to engage the sponsor contract manufacturing organization (CMO), who may subsequently propose actions based upon the DSMB's recommendation. Details of the DSMB communication plan can be found in the DSMB charter.

2.3.3 Estimated Treatment and Study 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 of the protocol. Patients with evidence of radiological PD who meet the criteria set forth in Section 10.3.2. of the protocol for *Treatment After Initial Radiological Progression* should continue treatment and be followed according to irRECIST, as described in Section 10.3.2 of the protocol. This study will be conducted at up to 30 centers in the United States.

2.3.4 Study Drug Treatment

A treatment cycle is defined as 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 AE. 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. Up to 120 patients with advanced epithelial ovarian cancer will be randomized to receive avelumab with entinostat or placebo in a 2:1 allocation in the Phase 2 Expansion Phase.

2.3.5 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. Therefore, the importance of timely and complete disease assessments in this study cannot be overstated. 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 at the discretion of the Investigator, as defined by irRECIST.

The same method of assessment and technique (e.g., CT scan or MRI) used to characterize each lesion at study screening must be used at each subsequent post-screening assessment. Post-screening scans and the corresponding overall tumor assessment (according to RECIST and irRECIST) should be performed prior to initiating the subsequent cycle to rule out PD that would warrant study treatment

discontinuation.

2.3.5.1 Tumor Measurement and Assessment

Initial tumor imaging at screening will 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. These initial scans may be assessed by the central imaging vendor. Patients will have radiological disease assessments performed every 6 weeks (± 3 days) (i.e., 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 should not be delayed for delays in treatment 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 a 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 within the electronic case report form (eCRF) according to 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 will be 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.

2.3.5.2 Disease Response Assessment Criteria

Patients will have radiological disease assessments performed every 6 weeks (± 3 days) (i.e., 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 then be done every 8 weeks (± 3 days) until unequivocal PD. Radiological assessments should be kept to the calendar schedule and not be delayed for missed study drug administration.

Partial response or CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date that 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 the response. Scans from non-responders may also be reviewed by the core radiologic laboratory at the direction of the Sponsor.

2.3.6 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 process that follows for assessing radiological PD will be used in this study.

If radiologic imaging demonstrates initial evidence for PD, tumor assessment should

be repeated 4 weeks at the earliest, 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, 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 2-2. 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 as described in the schedule of study (Protocol Table 1-1).

2.3.7 [redacted]

Blood

[redacted]

[redacted]

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. 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. 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]

2.3.8 Pharmacokinetic Assessments

Entinostat

Blood samples for determination of entinostat levels will be collected pre-dose and 2 to 4 hours post-dose on Cycle 1 Day 1; 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.

Avelumab

Blood samples for determination of avelumab levels and avelumab antidrug antibodies (ADAs) will be collected pre-dose and immediately prior to the end of infusion (PK only) on Day 1 of Cycles 1 through 6, then Day 1 of Cycles 8, 10, 12, 16, 20, 28, 32, 36, and 48, at EOT, and at the 30-day Follow-up. Samples 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 arm. 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.

2.3.9 Safety Assessments

The following assessments will be performed to evaluate the safety profile of entinostat and avelumab. The assessments will be performed during Screening, on Day 1 of each cycle, at the EOT visit (7 days post-last dose) and at the Safety Follow-up visits, as described in the Schedule of Study Assessments (Protocol Table 1-1).

- Vital signs: temperature, pulse rate, and blood pressure (systolic and diastolic)
- Body height (at screening only) and weight
- 12-lead Safety ECGs are recorded at the Screening Visit, and as clinically indicated throughout the study as outlined in the Schedule of Study Assessments
- AE and SAE recording
- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, platelet count, hemoglobin (HGB) and hematocrit (HCT), coagulation studies, including prothrombin time or international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT; at Screening only)
- Chemistry: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total bilirubin, blood

urea nitrogen (BUN), calcium, creatinine, electrolytes (sodium, potassium, magnesium [Mg at Screening only; thereafter as clinically indicated], chloride, bicarbonate), glucose, lactate dehydrogenase (LDH), phosphorus, total protein, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH; Screening only) and thyroxine (T4)

2.3.10 Other Assessments

Other assessments include patient demographics, epithelial ovarian cancer history, prior systemic anti-cancer therapy, prior surgery related to ovarian cancer, prior radiation therapy, medical history, physical examinations, entinostat administration and accountability, avelumab administration and accountability, concomitant medications and procedures, protocol deviations, post-treatment anti-cancer therapy, ECOG performance status score, and clinical disease assessment, collected per Schedule of Study Assessments (Protocol Table 1-1).

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

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.

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows. 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).

3.1.2 Reporting of Numerical Values

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of patients with non-missing assessments. If there are missing values, the number missing will be presented, but without a percentage.

Means and medians will be reported to one decimal place more than the data reported in the clinical data management system. Standard deviations will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same to the same number of decimal places displayed in the clinical data management system.

3.1.3 Baseline Value and Change from Baseline

Baseline will be defined as the most recent, non-missing value obtained immediately prior to the first dose of any study drug (entinostat or avelumab). Change from baseline will be calculated by subtracting the baseline value from the on-study assessment for each patient (i.e., post-dose – baseline).

3.1.4 Handling of Missing/Incomplete Values

Unless otherwise specified, missing data will not be imputed. For AE start dates, the first algorithm described below will be used to determine treatment emergence. For incomplete dates of diagnosis, the second algorithm described below will be used to determine the incomplete date if the day and/or month is missing.

Algorithm for Imputation of Incomplete/Missing Adverse Event Start Dates

Case 1:

if year portion of AE start date = missing then missing AE start date = dose date;

Case 2:

if year portion of AE start date = year portion of dose date

then do;

if month portion of AE start date = missing
then missing AE start date = dose date;

else if month portion of AE start date = month portion of dose date
then missing AE start date = dose date;

else if month portion of AE start date ≠ month portion of dose date
then missing AE start date = mdy(AE start month, 1, AE start year);

end;

Case 3:

If year portion of AE start date > year portion of dose date, then AE is treatment-emergent.

Algorithm for Imputation of Incomplete/Missing Date of Diagnosis

If the date of diagnosis is missing the day and/or month, the following algorithm will be used.

Case 1:

For cases where day and month are unknown or missing, the day and month will be set to June 30 with the known year, provided that the resulting date is before treatment start date. Otherwise, one day prior to treatment start date (treatment start date – 1) will be used.

Case 2:

For cases where only the day is unknown or missing, the day will be set to 15 with the non-missing month and year, provided the resulting date is before the treatment start date. Otherwise, one day prior to the treatment start date (treatment start date – 1) will be used.

3.2 Analysis Sets

3.2.1 Full Analysis Set

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 in Phase 2 by following intent-to-treat principle. Patients will be grouped according to the treatment group to which they were randomized (entinostat + avelumab or avelumab only). Patients in this set will be analyzed according to the treatment they were randomized to receive, regardless of any errors in dosing.

3.2.2 Per-Protocol Analysis Set

The Per-Protocol Analysis Set is a subset of the FAS. The Per-Protocol Analysis Set consists of all patients who do not violate the terms of the protocol in a way that would majorly impact the study outcome. All decisions to exclude patients for the Per-Protocol Analysis Set will be made prior to the unblinding of the treatment arms for the final analysis.

3.2.3 Safety Analysis Set

Without otherwise specified, 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 Analysis Set will include all patients who received at least one dose of either study drug, entinostat, or avelumab. Patients will be included in the treatment group corresponding to the study drug they actually received. For most patients this will be the treatment group to which they were randomized. Patients who took incorrect study drug for the entire treatment period will be included in the treatment group corresponding to the study drug they actually received. At least one laboratory or vital sign measurement obtained, subsequent to at least one dose of study treatment, is required for inclusion in the analysis of a safety specific parameter. To assess change from baseline, a baseline measurement is also required.

3.2.4 Pharmacokinetic Analysis Set

Patients will be evaluable for the primary PK analysis if they receive the reference agent administered with and without the other agent. Additionally, patients must have sufficient plasma concentration-time data from each treatment period in order to provide for meaningful assessment of the PK parameters (e.g., AUC and C_{max}). The PK Analysis Set will include all patients who have evaluable plasma concentration-time data for each treatment period, and for whom one or more of the designated PK parameters can be determined.

3.3 Analysis Variables

3.3.1 Efficacy Variables

Efficacy variables include:

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

3.3.2 Pharmacokinetic Variables

The following PK parameters for the plasma concentrations of entinostat or avelumab will be calculated via non-compartmental methods and summarized, where applicable, using the WinNonlin™ software package (WinNonlin™ Phoenix, Version 6.3, Pharsight Corporation, Mountain View, CA).

Pharmacokinetic variables include:

- C_{max}, maximum plasma concentration
- T_{max}, time at which maximum plasma concentration was observed
- AUC_{0-t}, area under the plasma concentration-time curve from time zero to the last measurable concentration
- AUC_{0-inf}, area under the plasma concentration-time curve from time zero extrapolated to infinity
- $t_{1/2}$, elimination half-life
- λ_z, terminal elimination rate constant

All measurable plasma concentrations will be used for the analysis. For concentration values reported as no Results/not Reportable (NR), values will be treated as missing. Values below the quantifiable limit (BQL) that occur prior to the first measurable concentration will be treated as zero. All other BQL values will be treated as missing.

The mean plasma concentration over time by treatment and the individual subject plasma concentration versus time data will be plotted. Nominal times will be used for plotting the mean plasma concentrations over time by treatment. Actual sampling times will be used for the individual figures and for the non-compartmental analysis.

3.3.3 Safety Variables

Safety variables include:

- Determination of DLT, MTD and RP2D
- Incidence of TEAEs:

  TEAEs are defined as any AE occurring or worsening in severity after the administration of study drug. TEAEs will be categorized as:

  - Relationship to entinostat
  - Relationship to avelumab
  - Severity/Grade according to National Cancer Institute Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03
  - Action with respect to entinostat
  - Action with respect to avelumab
  - Seriousness and outcome

- Change in chemistry and hematology parameters from baseline to minimum and maximum post-baseline values, average post-baseline value, and last post-baseline value
- Shifts in chemistry and hematology parameters from baseline to worst post-baseline in CTCAE toxicity grade
- Shifts in chemistry and hematology parameters outside the laboratory normal range from baseline to maximum increase and/or decrease, and last post-baseline value
- Change from baseline in vital signs and weight at each post-baseline time point
- Change from baseline in 12-lead ECG parameters at each post-baseline time point
- Change from baseline in ECOG at each post-baseline time point

3.3.4 Exploratory Variables

3.4 Disposition and Evaluability

3.4.1 Disposition

The number and percentage of patients who were screened, enrolled, dosed, and withdrew prior to receiving a dose (including reasons for not completing dosing), the number of cycles on treatment, the reason for screen failure, the reasons for discontinuation of each study treatment, the reason for discontinuation of the study, will be presented by dose cohort in Phase 1 and by treatment arm in Phase 2.

3.4.2 Protocol Deviations

Protocol deviations will be presented in a patient listing.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Demographics will be summarized by dose cohort for the Safety Analysis Set (Phase 1 only) and will be summarized by treatment arm for the FAS. Frequency statistics will be presented for sex, race, ethnicity, age group, and ECOG performance status at baseline. Summary statistics will be presented for age, weight (kg), height (cm), and body surface area (m^2).

Body surface area will be calculated using the Mosteller formula:

$$\text{Body surface area} = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

All demographic data will be presented in patient listings.

3.5.2 Ovarian Cancer Disease History

The following baseline disease characteristics variables will be summarized for the FAS:

- Time since initial diagnosis
- Disease stage at initial diagnosis

- Histopathological grade at initial diagnosis
- Time since diagnosis of advanced or metastatic ovarian cancer
- Metastatic sites

Disease history, including prior anti-cancer therapies, surgeries, and radiotherapy, will be summarized by dose cohort and by treatment arm for the Safety Analysis Set (Phase 1 only) and for the FAS, respectively. Frequency statistics will be presented for ECOG performance status, primary tumor location, [redacted], and disease status at enrollment. Summary statistics will be presented for years since diagnosis.

If the date of diagnosis is missing the day and/or month, the algorithm specified in Section 3.1.4 for incomplete dates will be used to determine the date and time since the study start.

All ovarian cancer disease history data will be presented in patient listings.

3.5.3 Medical History, Prior Medications, and Physical Exam

Data regarding medical history, prior medications, and clinically significant findings from the physical exam will be presented in patient listings for the Safety Analysis Set (Phase 1 only) and for the FAS.

3.6 Concomitant Medications

Any medication reported on the appropriate post treatment form (Concomitant Medications) will be considered concomitant.

All medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2016). The number and percentage of patients taking each concomitant medication will be presented by dose cohort (Phase 1) and treatment arm (Phase 2) for the Safety Analysis Set. All medication data will be listed individually and summarized by anatomical therapeutic class and generic name.

3.7 Treatment Exposure

The overall duration of study drug administration (in days) and the total number of cycles started will be tabulated for each patient and summarized for each study phase. The average dose administered and cumulative dose of entinostat administered (in mg)

will be calculated. These data will be further summarized by calculating the mean, standard deviation, median, and range of these values. The average proportion of the planned doses of study drug will be calculated for all patients. Similar analyses will be performed for avelumab administration (in mg/kg). The number and proportion of patients with one or more dosage modification (i.e., reduction or delay) of each study drug will be tabulated along with the reasons for dosage modification. The primary reason for study drug discontinuation will be tabulated in a similar manner. All treatment exposure data will be presented in patient listings for the Safety Analysis Set.

3.8 Efficacy Analysis

Efficacy analyses will be performed using the FAS and, where appropriate, the Per-Protocol Set. The efficacy outcomes for the 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. The calendar date of the 97th event will serve as the data cutoff date for the primary analysis. The primary analysis of the secondary endpoints, exploratory endpoints, and safety will occur at the time of the primary PFS analysis. An interim analysis is planned after 65 PFS failures (67% of total events) observed in Phase 2. 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 type I error for multiple testing of PFS. The details of alpha spending are described in Section 2.3.2.

Progression-free Survival

The primary efficacy endpoint is duration of PFS, defined as the number of months from randomization to PD or death due to any cause, whichever occurs first. Disease assessments will continue until PD, even after the originally assigned study treatment is discontinued. For purposes of analysis, 1 month is considered 30.4375 days. The duration of PFS as determined by RECIST 1.1 (Eisenhauer 2009) and irRECIST (Seymour 2017) will be summarized descriptively using the Kaplan-Meier method

(Kaplan 1958). Inferential comparisons between treatment arms will be made using the log rank test, stratifying on the randomization stratification factors. The Cox proportional hazard model (Cox 1972) with treatment as a factor, stratified by the stratification factors used in randomization, will be used to estimate the HR for treatment effect and corresponding 95% CI, without any other covariate adjustment. 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, the date of progression or censoring for PFS will be determined according to the conventions listed in Table 3-1.

All patients are to be followed for disease progression according to the protocol-specified schedule even after a non-protocol, anti-cancer therapy is started. For the primary analysis of PFS, documented disease progression (or death without prior disease progression) occurring after the start of such therapy will be considered as a PFS event.

Table 3-1. Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression or Censoring	Outcome
Documented disease progression	Date of disease assessment showing documented disease progression	Progressed
Death without documented progression	Date of death	Progressed
No baseline disease assessments	Date of randomization	Censored
No post-baseline assessment and no death	Date of randomization	Censored
Death or documented progression after more than one missed consecutive post-baseline disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the missed visit or date of randomization, whichever is later	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Patient lost to follow-up (or withdrew consent from study participation) before documented	Date of last disease assessment	Censored

progression or death		

Sensitivity Analyses of Progression-free Survival

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis by changing one or more of the censoring rules stated in the primary analysis (Table 3-1). The following sensitivity analyses will be performed for PFS:

Progression-free Survival Sensitivity Analysis 1 (forward-dating PFS assessment time)

A main source of potential bias for the PFS endpoint arises from differences between the actual and observed date of disease progression, particularly if the difference is systematically related to the patient's treatment arm. Deviations from scheduled assessment times may be due to 1) AEs causing delays on one treatment arm, 2) more frequent assessments in one treatment arm because of toxicity or worsening symptoms, 3) delay in assessments because patients are doing well.

To address the above concerns, analyses will be performed to identify asymmetry between treatment arms for the frequency of missed disease assessment times, and deviations between the actual and scheduled assessment times. Descriptive statistics of frequency of missed scheduled assessment, and deviation between actual and scheduled assessment time, will be summarized by treatment arm for FAS.

In addition to the above, the PFS analysis also will be re-run with the following modifications made to the progression and censoring dates for the following cases:

- For patients with disease progression that was documented between two scheduled disease assessments, the date of disease progression will be moved forward to the date of the next planned disease assessment.
- For patients without disease progression, and whose last disease assessment was between two scheduled assessments, the censoring date will be moved forward to the date of the next planned disease assessment.

The definition of PFS for this sensitivity analysis is presented in Table 3-2. Those items that differ from Table 3-1 are underlined.

Progression-free Survival Sensitivity Analysis 2 (Subsequent anti-cancer therapy as

a PFS event)

As noted previously, disease assessments will continue until disease progression, even after non-protocol anti-cancer therapy is started. It's anticipated that some patients may receive subsequent anti-cancer therapy prior to documentation of PD.

To assess the impact of subsequent anti-cancer therapy on the primary PFS analysis, the start of a new anti-cancer therapy will be considered as a PFS event in this sensitivity analysis. The start date of the new anti-cancer therapy will serve as the progression date.

The definition of PFS for sensitivity analysis is presented in Table 3-3. Those items that differ from Table 3-1 are underlined.

Progression-free Survival Sensitivity Analysis 3 (Censoring for subsequent anti-cancer therapy)

Another sensitivity analysis will be conducted to further evaluate the impact of subsequent anti-cancer therapy on the primary PFS analysis. For patients who started a new anti-cancer therapy prior to progression, including any post-discontinuation treatment therapy, PFS will be censored at the date of the last disease assessment before the new therapy was started, regardless of whether or not this patient subsequently experienced PD or death. The definition of PFS for this sensitivity analysis is presented in Table 3-4. Those items that differ from Table 3-1 are underlined.

Table 3-2. Progression-free Survival Sensitivity Analysis 1

Situation	Date of Progression or Censoring	Outcome
Documented disease progression	Date of disease assessment showing documented disease progression	Progressed
Death without documented progression	Date of death	Progressed
No baseline disease assessments	Date of randomization	Censored
No post-baseline assessment and no death	Date of randomization	Censored
Death or documented progression after more than one missed consecutive post-baseline disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the missed visit or date of randomization,	Censored

	whichever is later	
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last disease assessment	Censored
Documented disease progression between two scheduled disease assessments	Date of next scheduled disease assessment	Progressed
Alive and without documentation of disease progression and last disease assessment was between two scheduled assessments	Date of next scheduled disease assessment	Censored

Note: items that differ from Table 3-1 are underlined.

Table 3-3. Progression-free Survival Sensitivity Analysis 2

Situation	Date of Progression or Censoring	Outcome
Documented disease progression	Date of disease assessment showing documented disease progression	Progressed
Death without documented progression	Date of death	Progressed
No baseline disease assessments	Date of randomization	Censored
No post-baseline assessment and no death	Date of randomization	Censored
Death or documented progression after more than one missed consecutive post-baseline disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the missed visit or date of randomization, whichever is later	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last disease assessment	Censored
New anti-cancer treatment started	Date of the new anti-cancer treatment started	Progressed

Note: items that differ from Table 3-1 are underlined.

Table 3-4. Progression-free Survival Sensitivity Analysis 3

Situation	Date of Progression or Censoring	Outcome
Documented disease progression	Date of disease assessment showing documented disease progression	Progressed
Death without documented progression	Date of death	Progressed
No baseline disease assessments	Date of randomization	Censored
No post-baseline assessment and no death	Date of randomization	Censored
Death or documented progression after more than one missed consecutive post-baseline disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the missed visit or date of randomization, whichever is later	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last disease assessment	Censored
New anti-cancer treatment started	Date of last disease assessment visit without documentation of disease progression that is before the start of new anti-cancer treatment	Censored

Note: items that differ from Table 3-1 are underlined.

Objective Response Rate

Objective 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. Tumor response will be assessed using RECIST 1.1 and irRECIST, as outlined in Protocol Section 5.1. Approximate 95% confidence intervals (CIs) 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 and Time to Response

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 the PR or CR (whichever response occurs first and subsequently confirmed), to the first date that recurrent disease or PD is documented. The same analysis will be repeated for patients who achieve immune-related CR (irCR) or immune-related PR (irPR). The date of progression or censoring for DOR will be determined according to the conventions listed Table 3-5. These conventions are based on the May 2007 FDA Guidance for Industry, '*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*'. DOR will be summarized descriptively using the Kaplan-Meier method.

Table 3-5. Date of Progression or Censoring for Duration of Response

Situation	Date of Progression or Censoring	Outcome
Documented disease progression	Date of disease assessment showing documented disease progression	Progressed
Death without documented progression	Date of death	Progressed
Death or progression after more than one missed disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the missed visit	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored

Time to response will be calculated for patients who achieve a CR or PR. For such patients, TTR is defined as the number of months from the randomization date to the first date the patient achieved a PR or CR (whichever response occurs first and was subsequently confirmed). The same analysis will be repeated for patients who achieve irCR or irPR.

Clinical Benefit Rate

Clinical benefit rate, as determined by RECIST 1.1, 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 a CR, PR, or SD lasting for at least 6 months. Stable

disease will be measured from the start date of study treatment until the criteria for PD is first met. The analysis of CBR and its duration will be based on the methods described above for ORR and DOR, respectively. Approximate 95% CIs will be calculated by treatment arm for the CBR. The comparison of the observed CBRs 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. Clinical benefit rate, as determined by irRECIST, 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 an irCR, irPR, or irSD, lasting for at least 6 months. The analysis of CBR, based on irRECIST, will follow the same method described above.

Overall Survival

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 the 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. The duration of OS will be summarized descriptively using the Kaplan-Meier method with 95% CIs, calculated using Greenwood's formula. For the primary analysis of OS, the difference in treatment effect will be tested using the stratified log rank test, stratifying on the randomization stratification factors. 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 across randomization strata will be examined by Wald's test using a two-sided significance level of 0.05.

To supplement the above analysis of OS, a summary of the anti-cancer therapies, and interventions received following the discontinuation of study treatment, will be provided. Such therapies will be collected during the scheduled post-treatment, follow-up assessments. The therapies will be summarized by treatment arm and will be classified as chemotherapy, hormonal therapy, radiation, surgery, maintenance or other.

3.9 Subgroup and Multivariate Analyses

Supportive analyses will be performed to determine whether the estimated treatment effect that is observed for the primary analysis of PFS is consistent across selected subgroups of patients. The HR (or odds ratio) for treatment effect will be estimated within each subgroup. If a subgroup consists of fewer than 10% of Phase 2 randomized patients, analysis within that subgroup will be omitted. Forest plots will be used to display the HRs and 95% CIs across subgroups. Kaplan-Meier figures may be provided for each treatment arm within each subgroup.

The results of the subgroup analyses will be ordered according to the hierarchy listed below (Tier 1 and Tier 2). The hierarchy was determined according to the baseline factor's relative prognostic importance for patients with advanced epithelial ovarian cancer. Tier 1 represents the subset of baseline factors with the greatest anticipated prognostic importance, etc.

Tier 1 *subgroup analyses:*

- Presence of bulky disease (defined as presence of a tumor ≥ 50 mm) (yes vs. no)
- Platinum based therapy (resistant, refractory and sensitive)
- History of progression while on primary platinum treatment or within 1 month from completion of primary platinum-containing regimen versus not
- Number of prior platinum-based therapies (< 2, ≥ 2)
- Disease stage at initial diagnosis (stage II, stage III/locally advanced, stage IV)
- [redacted]
- [redacted]

Tier 2 *subgroup analyses:*

- Prior anti-cancer therapies
- Prior therapy for advanced disease (yes, no)

- Prior adjuvant/neoadjuvant therapy (yes, no)
- Prior chemotherapy (yes, no)
- Prior radiation therapy (yes, no)
- Race (Caucasian, all others)
- Age group at initial diagnosis (< 65, ≥ 65 years)
- Age group at study entry (< 65, ≥ 65 years)
- ECOG performance status at study entry (0, 1)
- Body mass index (BMI) at study entry (< 30, ≥ 30)

3.10 Safety Analysis

Safety analyses will be performed on the Safety Analysis Set.

3.10.1 Adverse Events

An AE is defined 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. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not the AE is related to the medicinal (investigational) product. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant as determined by the Investigator.

Analyses of AEs will be based on the principle of treatment emergence. Treatment-emergent AEs are defined as having onset after study drug dosing or a sign, symptom, or diagnosis that worsens after study drug dosing. Henceforth, whenever an analysis or summary of AEs is mentioned, it is intended that this is in reference to TEAEs, unless it is stated otherwise.

If AE start dates are completely missing or partially missing, the date imputation rules described previously in Section 3.1.4 will be applied for the determination of treatment-emergence. This algorithm will be used only if the end date of the AE (if reported) indicates the event was not resolved before the first administration of study drug. Imputed AE dates will not be used to calculate the duration of AE episodes.

All AEs will be coded according to System Organ Class (SOC) and Preferred Term

(PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 19.0 or later).

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.

A summary of AEs, including incidences of:

- AEs
- SAEs
- AEs related to entinostat ("possibly related" or "related")
- AEs related to avelumab ("possibly related" or "related")
- AEs related to any study drug
- SAEs related to entinostat, avelumab, or both
- AEs leading to dose modification of entinostat, avelumab, or both
- AEs leading to discontinuation of entinostat, avelumab, or both
- AEs with a fatal outcome
- AEs with a CTCAE severity grade of Grade 3 or greater
- AEs with CTCAE severity of Grade 3 or greater related to entinostat, avelumab, or both

will be presented by dose cohort in Phase 1 and by treatment arm in Phase 2.

Incidences of all AEs will be presented by SOC and PT by dose cohort in Phase 1 and by treatment arm in Phase 2. SOCs will be sorted alphabetically. Within an SOC, PTs will be presented by decreasing incidence overall. Incidences of SAEs, and incidence of related SAEs by PT only, will be presented by decreasing incidence overall.

Incidence of AEs will also be presented by PT and severity, and by PT and relationship to study drug. Incidence of AEs of Grade 3 or greater, and incidence of related AEs of Grade 3 or greater, will also be presented by PT. For patients experiencing the same PT at multiple severities, the occurrence of the AEs with the greatest severity will be used in the analysis of incidence by severity. For patients experiencing the same PT at multiple relationship levels, the occurrence of the AEs with the strongest relationship to study drug will be used in the analysis of incidence by relationship to study drug.

All reported AEs, regardless of whether they were treatment-emergent, will be included in patient listings. Listings of all SAEs and AEs leading to discontinuation of entinostat, avelumab, or both will also be provided.

3.10.2 Laboratory Evaluations

Hematology and serum chemistries will be summarized using summary statistics for the following values by cohort and overall: baseline value, minimum and maximum post-baseline values, average post-baseline value, and last post-baseline value. Change from baseline for each of these post-baseline values will also be summarized.

Whenever available, laboratory values will be assigned toxicity grades using the NCI-CTCAE, version 4.03. Shifts in laboratory values to outside the local laboratory normal range will be evaluated for selected laboratory tests by assessing, relative to the baseline value, the maximum increase and/or decrease observed throughout the course of study treatment, and the last reported value. The number and proportion of patients with directional shifts above or below the normal range will be summarized for selected laboratory tests. Similar analyses will be performed for shifts in NCI CTCAE toxicity grades relative to the baseline toxicity grade.

Percentages will be based on the total number of patients with a baseline assessment and at least one post-baseline assessment for the given laboratory parameter. Laboratory test groupings and standard normal ranges are described in Appendix 5.1, and CTCAE toxicity grades for hematology and chemistry parameters are described in Appendix 5.2 and Appendix 5.3, respectively.

Listings of all clinical laboratory data for each patient will be provided. A separate listing of all out of normal range as well as all toxicity grade values will also be provided.

3.10.3 Vital Signs

Change from baseline for vital signs (temperature, pulse, systolic/diastolic blood pressure, respiration rate, and weight) will be summarized over time by treatment group and overall.

A patient listing of all vital sign assessments will be provided.

3.10.4 ECG

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 where ECGs were assessed.

3.11 Pharmacokinetic Analysis

A population PK analysis will be used to describe the PK of entinostat. The effects of patient factors (e.g., demographics, clinical chemistries, and 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.

3.12 Correlative Analysis

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, 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).

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5 APPENDIX

5.1 Laboratory Test Groupings and Standard Normal Range

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Hematology, WBC with Differential				
WBC count‡	10^9 cells/L	XX.X	Decrease	3.2 – 9.8
Basophil count	10^6 cells/L	XX	Decrease	15 – 50
Eosinophil count	10^6 cells/L	XXX	Decrease	50 – 250
Lymphocyte count‡	10^6 cells/L	XXXX	Decrease	1500 – 3000
Monocyte count	10^6 cells/L	XXX	Decrease	285 – 500
Neutrophil count‡	10^6 cells/L	XXXX	Decrease	3000 – 5800
Lab group = Hematology, Erythrocytes and Platelets				
Hematocrit	Fraction of 1.00	0.XX	Decrease	0.33 – 0.43 (female)
				0.39 – 0.49 (male)
Hemoglobin‡	g/L	XXX	Decrease	115 – 155 (female)
				140 – 180 (male)
RBC count	10^{12}/L	X.X	Decrease	3.5 – 5.0
Platelet count‡	10^9/L	XXX	Decrease	130 – 400
Lab group = Hematology, Coagulation				
PT	seconds	XX	Increase	9 – 12
PTT‡	seconds	XX	Increase	22 – 37

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing. Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

Laboratory Test Groupings and Standard Normal Range (continued)

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Chemistry, Hepatic				
Albumin‡	g/L	XX	Decrease	40 – 60
Alk Phos‡	U/L	XXX	Increase	30 – 120
ALT‡	U/L	XXX	Increase	0 – 35
AST‡	U/L	XXX	Increase	0 – 35
Lactic dehydrogenase	U/L	XXX	Increase	50 – 150
Total Bilirubin‡	micromol/L	XX	Increase	2 – 18
Total Protein	g/L	X.XX	Decrease	60 – 80
Lab group = Chemistry, Renal				
BUN	mmol/L of urea	X.X	Increase	3.0 – 6.5
Creatinine‡	micromol/L	XXX	Increase	50 – 110
Creatinine clearance	mL/min	XXX	Decrease	75 – 125

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing.

Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

Laboratory Test Groupings and Standard Normal Range (continued)

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Chemistry, Electrolytes				
Bicarbonate‡	mmol/L	XX	Both	22 – 28
Calcium‡	mmol/L	X.XX	Both	2.20 – 2.56
Chloride	mmol/L	XXX	Both	95 – 105
Magnesium‡	mmol/L	X.XX	Both	0.80 – 1.20
Phosphorus	mmol/L	X.XX	Both	0.80 – 1.60
Potassium‡	mmol/L	X.X	Both	3.5 – 5.0
Sodium‡	mmol/L	XXX	Both	135 – 147
Lab group = Chemistry, Metabolic				
Glucose‡	mmol/L	XX.X	Both	3.9 – 6.1
Uric Acid	micromol/L	XXX	Increase	120 – 420

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing.

Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

5.2 CTCAE Toxicity Grades: Hematology

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		WBC with Differential	
WBC count	10^9/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 3.0 × 10^9/L
			Grade 2: < 3.0 – 2.0 × 10^9/L
			Grade 3: < 2.0 – 1.0 × 10^9/L
			Grade 4: < 1.0 × 10^9/L
Lymphocyte count	10^6 cells/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 0.8 × 10^6/L
			Grade 2: < 0.8 – 0.5 × 10^6/L
			Grade 3: < 0.5 – 0.2 × 10^6/L
			Grade 4: < 0.2 × 10^6/L
Neutrophil count	10^6 cells/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 1.5 × 10^6/L
			Grade 2: < 1.5 – 1.0 × 10^6/L
			Grade 3: < 1.0 – 0.5 × 10^6/L
			Grade 4: < 0.5 × 10^6/L

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

CTCAE Toxicity Grades: Hematology (continued)

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Erythrocytes and Platelets	
Hemoglobin	g/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 100 g/L
			Grade 2: < 100 – 80 g/L
			Grade 3: < 80 g/L
			Grade 4: Not defined
Platelet count	10^9/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 75 × 10^9/L
			Grade 2: < 75 – 50 × 10^9/L
			Grade 3: < 50 – 25 × 10^9/L
			Grade 4: < 25 × 10^9/L
		Coagulation	
PTT	seconds	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN– 1.5 × ULN
			Grade 2: > 1.5 – 2.5 × ULN
			Grade 3: > 2.5 × ULN
			Grade 4: Not defined

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

5.3 CTCAE Toxicity Grades: Chemistry

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Hepatic	
Albumin	g/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 30 g/L
			Grade 2: < 30 – 20 g/L
			Grade 3: < 20 g/L
			Grade 4: Not defined
Alk Phos	U/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 2.5 × ULN
			Grade 2: > 2.5 – 5.0 × ULN
			Grade 3: > 5.0 – 20.0 × ULN
			Grade 4: > 20.0 × ULN
ALT	U/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 3.0 × ULN
			Grade 2: > 3.0 – 5.0 × ULN
			Grade 3: > 5.0 – 20.0 × ULN
			Grade 4: > 20.0 × ULN

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

CTCAE Toxicity Grades: Chemistry (continued)

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Hepatic (continued)	
AST	U/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 3.0 × ULN
			Grade 2: > 3.0 – 5.0 × ULN
			Grade 3: > 5.0 – 20.0 × ULN
			Grade 4: > 20.0 × ULN
Total Bilirubin	micromol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 1.5 × ULN
			Grade 2: > 1.5 – 3.0 × ULN
			Grade 3: > 3.0 – 10.0 × ULN
			Grade 4: > 10.0 × ULN
		Renal	
Creatinine	micromol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 1.5 × ULN
			Grade 2: > 1.5 – 3.0 × ULN
			Grade 3: > 3.0 – 6.0 × ULN
			Grade 4: > 6.0 × ULN

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

CTCAE Toxicity Grades: Chemistry (continued)

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Electrolytes	
Sodium	mmol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 150 mmol/L
			Grade 2: > 150 – 155 mmol/L
			Grade 3: > 155 – 160 mmol/L
			Grade 4: > 160 mmol/L
		Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 130 mmol/L
			Grade 2: Not defined
			Grade 3: < 130 – 120 mmol/L
			Grade 4: < 120 mmol/L
Potassium	mmol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 5.5 mmol/L
			Grade 2: > 5.5 – 6.0 mmol/L
			Grade 3: > 6.0 – 7.0 mmol/L
			Grade 4: > 7.0 mmol/L
		Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 3.0 mmol/L
			Grade 2: Not defined
			Grade 3: < 3.0 – 2.5 mmol/L
			Grade 4: < 2.5 mmol/L

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

CTCAE Toxicity Grades: Chemistry (continued)

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Electrolytes (continued)	
Magnesium	mmol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 1.23 mmol/L
			Grade 2: Not defined
			Grade 3: > 1.23 – 3.30 mmol/L
			Grade 4: > 3.30 mm/L
		Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 0.5 mmol/L
			Grade 2: < 0.5 – 0.4 mmol/L
			Grade 3: < 0.4 – 0.3 mmol/L
			Grade 4: < 0.3 mmol/L
Calcium	mmol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 2.9 mmol/L
			Grade 2: > 2.9 – 3.1 mmol/L
			Grade 3: > 3.1 – 3.4 mmol/L
			Grade 4: > 3.4 mmol/L
		Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 2.0 mmol/L
			Grade 2: < 2.0 – 1.75 mmol/L
			Grade 3: < 1.75 – 1.5 mmol/L
			Grade 4: < 1.5 mmol/L

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

CTCAE Toxicity Grades: Chemistry (continued)

Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v4.03)
		Electrolytes (continued)	
Bicarbonate*	mmol/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 16.0 mmol/L
			Grade 2: < 16.0 – 11.0 mmol/L
			Grade 3: < 11.0 – 8.0 mmol/L
			Grade 4: < 8.0 mmol/L
Phosphorus	mmol/L	Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 0.8 mmol/L
			Grade 2: < 0.8 – 0.6 mmol/L
			Grade 3: < 0.6 – 0.3 mmol/L
			Grade 4: < 0.3 mmol/L
		Metabolic	
Glucose	mmol/L	Increase	Grade 0: ≤ ULN
			Grade 1: > ULN – 8.9 mmol/L
			Grade 2: > 8.9 – 13.9 mmol/L
			Grade 3: > 13.9 – 27.8 mmol/L
			Grade 4: > 27.8 mmol/L
		Decrease	Grade 0: ≥ LLN
			Grade 1: < LLN – 3.0 mmol/L
			Grade 2: < 3.0 – 2.2 mmol/L
			Grade 3: < 2.2 – 1.7 mmol/L
			Grade 4: < 1.7 mmol/L

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

*Bicarbonate toxicity grade are taken from CTCAE v3.0.

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