NCT #: NCT02437136

Syndax Pharmaceuticals

STATISTICAL ANALYSIS PLAN

A Phase 1b/2, Open-label, Dose Escalation Study of Entinostat in Combination with Pembrolizumab in Patients with Non-small Cell Lung Cancer, with Expansion Cohorts in Patients with Non-small Cell Lung Cancer, Melanoma, and Mismatch Repair-Proficient Colorectal Cancer

SNDX-275-0601

SAP Version:	Date of Statistical Analysis Plan:
Version 1.0	30 July 2019
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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	adverse event
ADA	antidrug antibody
ADaM	Analysis Dataset Model
$AUC_{0\text{-}inf}$	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
CBR	clinical benefit rate
CEA	Cancer Embryonic Antigen
CI	confidence interval
C_{max}	maximum plasma concentration
CR	complete response
CRC	colorectal cancer
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMIC	entinostat monotherapy immune correlate

Abbreviation	Full Term
EOT	End of Treatment
FAS	Full Analysis Set
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
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NR	no results/not reportable
NSCLC	Non small cell lung cancer
ORR	objective 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

Abbreviation	Full Term
PPI	Proton Pump Inhibitor
PR	partial response
PT	preferred term
PT/INR	prothrombin time or international normalized ratio
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
TCR	T cell receptor
TEAE	treatment-emergent adverse event
T_{max}	time at which maximum plasma concentration was observed
TSH	thyroid stimulating hormone
TTR	time to response
WHO	World Health Organization
λ_z	terminal elimination rate constant

1 INTRODUCTION

Clinical Trial SNDX-275-0601 is an open-label Phase 1b/2 evaluating the combination of entinostat with pembrolizumab in patients with advanced metastatic or recurrent NSCLC, melanoma, or mismatch repair-proficient colorectal cancer. The study has 2 phases, a Dose Escalation/Confirmation Phase (Phase 1b) and an Expansion Phase (Phase 2), with the Expansion Phase utilizing a Simon 2-stage design (Simon 1989) for each cohort. An additional cohort (Entinostat Monotherapy Immune Correlate [EMIC] Cohort) evaluating single agent entinostat followed by the combination will also be evaluated in patients with NSCLC in the Phase 2 expansion phase.

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-275-0601. The statistical methods and analyses described here are based on those presented in the study protocol. Any changes made to the planned analyses after this document has been finalized will be noted in the clinical study report.

This version of the SAP was written in accordance with the following protocol versions:

Table 1-1 Protocol Versions

Protocol	Version Date
Original	08-April-2015
Amendment #1	05-June-2015
Amendment #2	04-April-2016
Amendment #3	23-February-2017
Amendment #4	25-August-2017
Amendment #5	12-April-2018

The first patient was enrolled under the original protocol dated 08-April-2015. Since then, study 601 has undergone 5 amendments (Table 1).

For Amendment #1, significant changes include, addition of exploratory endpoint, the clarification of duration of therapy, clarification of the number of patients enrolled, modification of the language to include a definition of a DLT-evaluable patient, and the definition of DLT.

Amendment #2 clarified the process of deciding on the Recommended Phase 2 Dose (RP2D), updated the Adverse Events terms of attribution/relatedness, updated the dose modification requirements for entinostat.

Amendment #3 added an additional cohort of patients: Mismatch Repair-Proficient Colorectal Cancer and updated pembrolizumab background information

Amendment #4 increased the sample size for Cohorts 2 and 3 and modified the corresponding statistical considerations accordingly (Section 12 of the protocol), removed Proton Pump Inhibitors (PPIs) from the list of medications to be avoided, and modified Eligibility Criteria to clarify prior disease progression on immunotherapy.

Amendment #5 increased the sample size for Cohort 4 and modified the corresponding statistical considerations accordingly (Section 12 of the protocol), updated the standard language regarding pembrolizumab, clarified the description of the irRECIST process for assessment of disease progression for imaging and treatment after first radiologic evidence of progressive disease.

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

2.1.1 Primary Objectives

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

Phase 2 (Expansion Cohorts): To evaluate the preliminary efficacy of entinostat at the RP2D in combination with pembrolizumab in patients with melanoma, non-small cell lung cancer (NSCLC), and mismatch repair-proficient colorectal cancer (CRC), as determined by overall response rate (ORR), per the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in each cohort evaluated.

2.1.2 Secondary Objectives

Efficacy: To evaluate the efficacy of entinostat in combination with pembrolizumab in patients with melanoma NSCLC, and mismatch repair-proficient colorectal cancer as determined by secondary measures of efficacy per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) including:

- Clinical benefit rate (CBR) (complete response [CR]+partial response [PR]+stable disease [SD]) at 6 months
- Progression-free survival (PFS) status at 6 months
- PFS
- Overall survival (OS)

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

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

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

2.1.3 Exploratory Objectives

[redacted]

2.2 STUDY ENDPOINTS

2.2.1 Primary Efficacy Endpoint

- ORR, as determined by irRECIST

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

An analysis of efficacy endpoints will be performed with response determined using irRECIST, as well as RECIST version 1.1.

- CBR (i.e., CR+PR+SD at 6 months)
- PFS status at 6 months
- PFS
- OS

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

- DOR
- TTR

Safety:

- Determination of DLTs, MTD, and RP2D (in Phase 1 only)
- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs resulting in the permanent discontinuation of study drug, and deaths occurring within 90 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

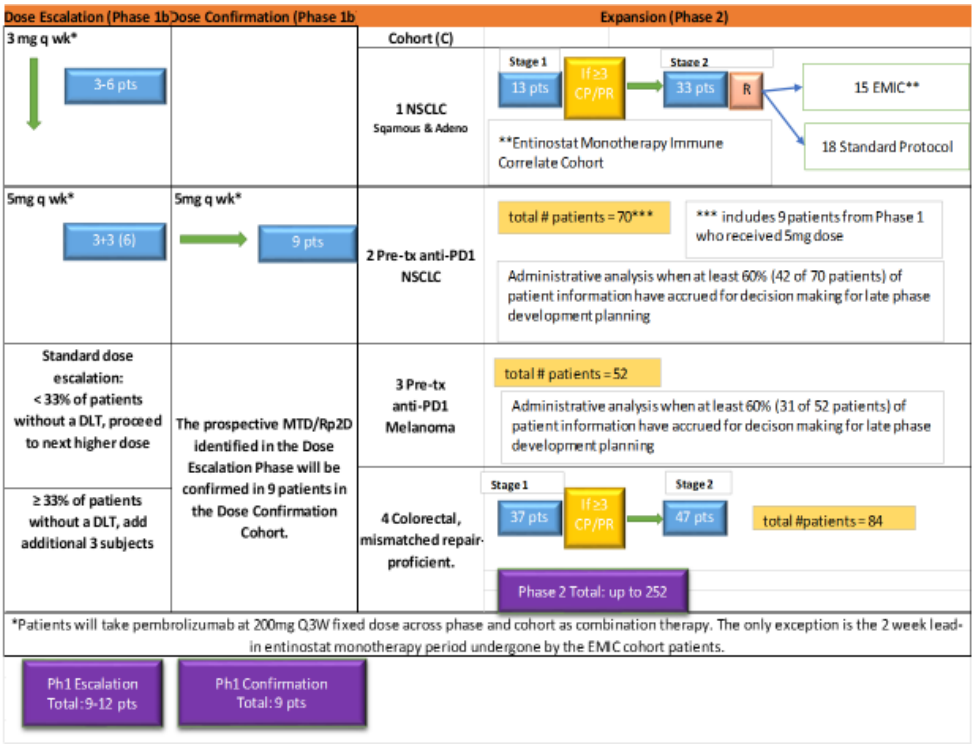
2.2.3 Exploratory Endpoints

[redacted]

2.3 STUDY DESIGN

Study SNDX-275-0601 is an open-label, Phase 1b/2 study evaluating the combination of entinostat plus pembrolizumab in patients with advanced metastatic or recurrent NSCLC, CRC, or melanoma. The study has 2 phases, a Dose Escalation/Confirmation Phase (Phase 1b) and an Expansion Phase (Phase 2), with the Expansion Phase utilizing a Simon 2-stage design (Simon 1989) for each cohort. An additional cohort (Entinostat Monotherapy Immune Correlate Cohort (EMIC)) evaluating single agent entinostat followed by the combination in patients with NSCLC will also be evaluated in the Phase 2 Expansion Phase. The study schema is presented in Figure 2-1.

Figure 2-1:



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

A cycle is 21 days in length. During treatment, patients will attend study center visits and have study evaluations performed on C1D1, C1D8, and C1D15; D1 and D15 of C2; and on D1 of each cycle thereafter. Patients will have radiological disease assessments performed during screening and every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment. The maximum duration of treatment for this study is planned to be 2 years. Disease will be assessed by computed tomography (CT), magnetic resonance imaging (MRI), and bone scans, as appropriate, and response will be assessed by the Investigator using irRECIST. Safety will be assessed during the study by documentation of AEs, clinical laboratory tests, physical examination, vital sign measurements, ECGs, and Eastern Cooperative Oncology Group (ECOG) performance

status. If a patient permanently discontinues 1 of the 2 study drugs (either entinostat or pembrolizumab), the patient may continue to receive monotherapy for up to 2 years, unless alternate therapy is started or another discontinuation criterion is met. After discontinuation of both study drugs, patients will complete an End of Treatment (EOT) visit within 7 days after the last study drug dose and Safety Follow-up visits 30 days and 90 days thereafter. After completion of the 30-day Safety Follow-up (F/U) visit, patients who have not experienced progressive disease (PD) are to be followed every 2 months until PD and every 3 months thereafter until death or closure of the study by the Sponsor. Collection of fresh tumor tissue core biopsy (image-guided if applicable) and blood samples are outlined in Section 5.1 of the protocol.

2.3.1 Number of Patients and Sample Size Considerations

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

Three to 6 patients will be enrolled in each dose cohort based on a standard Phase 1 dose escalation scheme. Each patient will participate in only 1 dose cohort. The total number of patients to be enrolled in the Dose Escalation/Confirmation 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 escalations required to achieve the MTD or RP2D.

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

A total of 9 additional patients will be enrolled in the Dose Confirmation Cohort to obtain additional AE, immune correlate, and anti-tumor activity data on entinostat at the MTD or RP2D in combination.

Phase 2/Expansion Phase:

In the Expansion Phase of the study, the safety and preliminary antitumor activity of entinostat when administered at the RP2D with pembrolizumab will be explored in up to 4 cohorts of adult solid tumors as previously defined. Up to 252 patients are planned to be enrolled among the 4 cohorts. Patients will be enrolled in each cohort according to a single-arm study design with ORR, as determined by irRECIST, as the primary endpoint. The Expansion Phase will be carried out in 2 stages so that enrollment for 1 or more of the cohorts evaluated can terminate early in the event the antitumor activity of the combination regimen is not sufficient. The decision to terminate or continue enrollment for each cohort will be made independently of the other. The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage, as described for cohorts 1, 2 and 3, was determined based on the optimum version of Simon's 2-stage design (Simon 1989), with 80% power and 1-sided significance level of 10%. For cohort 4, the number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage was determined based on the optimum version of Simon's 2-stage design, with 90% power and 1-sided significance level of 5%.

Cohort 1 (NSCLC patients with squamous cell and adenocarcinoma histology who have not been previously treated with a PD-1 or PD-L1-blocking antibody)

A maximum of 46 patients will be enrolled in Cohort 1. A true ORR of 35% is hypothesized. An ORR greater than 20% is considered a lower threshold for antitumor activity that would warrant continued development. Based on the design elements specified above, up to 13 patients may be enrolled for either tumor type during the first stage; if 2 or fewer patients achieve an objective response (CR or PR), confirmed or unconfirmed, then enrollment will terminate; otherwise, 33 additional patients will be enrolled during the second stage. Upon completion of the second stage, if 13 or more patients out of the 46 enrolled achieve CR or PR, then the true ORR for the combination therapy likely exceeds 20%, the lower threshold of acceptable antitumor activity. Alternatively, if 12 or fewer patients achieve an objective response at the end of the second stage, then the true ORR is likely 20% or lower, and further evaluation of the

combination therapy may not be pursued for that tumor type. If the true ORR is 20% or less for a tumor type, then the expected sample size is 29.4, with probability of terminating enrollment at the end of the first stage equal to 50%.

Cohort 2 (Patients with NSCLC (any histology) who have previously been treated and progressed on a PD-1 or PD-L1-blocking antibody)

A maximum of 56 patients will be enrolled in Cohort 2. A true ORR of 15% is hypothesized. A response rate greater than 5% is considered the lower threshold for antitumor activity that would warrant continued development in this setting. Based on the design elements specified above, up to 20 patients may be enrolled during the first stage: if 1 or no patients achieve a CR or PR, confirmed or unconfirmed then enrollment will terminate; otherwise 36 additional patients will be enrolled during the second stage. Upon completion of the second stage, if 5 or more patients out of 56 enrolled achieve CR or PR, then true ORR for the combination regimen likely exceeds 5%, the lower threshold of acceptable antitumor activity. Alternatively, if 4 or fewer patients achieve an objective response at the end of the second stage, then the true ORR is likely 5% or lower and further evaluation of the combination therapy may not be pursued in this setting. If the true ORR is 5% or less, then the expected sample size is 29.5, with probability of terminating enrollment at the end of the first stage equal to 74%. However, with Amendment 5, the study design for this cohort is changed from Simon 2-stage design to single proportional binomial test after moving in to 2^{nd} stage. Based on single proportional binomial test, maximum of 70 patients are enrolled in Cohort 2.

Ninety-six percent 1-sided confidence interval (or 92% 2-sided confidence interval) of the observed one sample proportion will be calculated. The trial will be considered a success if the lower limit of 96% confidence interval is greater than 5%.

Syndax will conduct one administrative analysis when at least 60% (42 out of 70 patients) of patient information has been accrued in cohort 2 for decision making for late phase development planning. This administrative look will not lead to stopping of the study. Nonetheless, 0.01 alpha is being allocated for the first administrative look, leaving 0.04 alpha for the final analysis.

Cohort 3 (Patients with melanoma who have previously been treated and progressed on a PD-1 or PD-L1-blocking antibody)

A maximum of 34 patients will be enrolled in Cohort 3. A true ORR of 25% is hypothesized. A response rate greater than 10% is considered the lower threshold for antitumor activity that would warrant continued development in this setting. Based on the design elements specified above, up to 13 patients may be enrolled during the first stage: if 1 or no patients achieve a CR or PR, confirmed or unconfirmed then enrollment will terminate; otherwise 21 additional patients will be enrolled during the second stage. Upon completion of the second stage, if 6 or more patients out of 34 enrolled achieve CR or PR, then true ORR for the combination regimen likely exceeds 10%, the lower threshold of acceptable antitumor activity. Alternatively, if 5 or fewer patients achieve an objective response at the end of the second stage, then the true ORR is likely 5% or lower and further evaluation of the combination therapy may not be pursued in this setting. If the true ORR is 10% or less, then the expected sample size is 20.9, with probability of terminating enrollment at the end of the first stage equal to 62%. However, with Amendment 5, the study design for this cohort is changed from Simon 2-stage design to single proportional binomial test after moving in to 2nd stage. Based on single proportional binomial test, maximum of 52 patients are enrolled in Cohort 3. Ninety-six percent 1-sided confidence interval (or 92% 2-sided confidence interval) of the observed one sample proportion will be calculated. The trial will be considered a success if the lower limit of 96% confidence interval is greater than 10%. Syndax will conduct one administrative analysis when at least 60% (31 out of 52 patients) of patient information has been accrued in cohort 3 for decision making for late phase development planning. This administrative look will not lead to stopping of the study. Nonetheless, 0.01 alpha is being allocated for the first administrative look, leaving 0.04 alpha for the final analysis.

Cohort 4 (Patients with CRC who have not previously been treated on a PD-1 or PD-L1-blocking antibody)

A maximum of 84 patients will be enrolled in Cohort 4. A true ORR of 15% is hypothesized. An ORR greater than 5% is considered the lower threshold for antitumor

activity that would warrant continued development in this setting. Based on the optimum version of Simon's 2-stage design, with 90% power and 1-sided significance level of 5%, up to 37 patients may be enrolled during the first stage: if fewer than or equal to 2 patients achieve a CR or PR, confirmed or unconfirmed, then enrollment will terminate; otherwise, 47 additional patients will be enrolled during the second stage. Upon completion of the second stage, if 8 or more patients of the 84 enrolled achieve CR or PR, then the true ORR for the combination regimen likely exceeds 5%, the lower threshold of acceptable antitumor activity. Alternatively, if 7 or fewer patients achieve an objective response at the end of the second stage, then the true ORR is likely 5% or lower and further evaluation of the combination therapy may not be pursued in this setting. If the true ORR is 5% or less, then the expected sample size is 50.2, with probability of terminating enrollment at the end of the first stage equal to 72%.

2.3.2 Estimated Treatment and Study Duration

The maximum duration of treatment for this study is planned to be 35 cycles (approximately 2 years.)

Patients who complete C1 may continue on study as long as, in the Investigator's judgment, the patient is tolerating the study treatment, is not at an increased safety risk, and continues to meet protocol eligibility criteria.

If a patient permanently discontinues 1 of the 2 study drugs (either entinostat or pembrolizumab), the patient may continue to receive monotherapy for up to 2 years, unless alternate therapy is started or another discontinuation criterion is met (Section 10 of the protocol).

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 study drug dose and Safety Follow-up visits 30 days (+/- 3 days) and 90 days (+/- 3 days) thereafter. After completion of the 30-day Safety F/U visit, patients who have not experienced PD are to be followed every 2 months until PD and every 3 months thereafter until death or closure of the study by the

Sponsor. The purpose of the post-treatment follow-up is to ascertain the duration of PFS for all patients in the study. After development of PD, surviving patients are to be followed on an every 3-month basis for alternate therapy and survival until closure of the study. Up to approximately 40 study centers are planned to be recruited for participation in this study.

2.3.3 Study Drug Treatment

Entinostat

Patients will receive entinostat in an open-label fashion; the dose for an individual patient is dependent on the cohort/study phase in which the patient is enrolled (Section 8.2.1.1 of the protocol).

The dose of entinostat is dependent on the cohort / study phase in which the patient is enrolled. In the Dose Escalation Phase, the planned entinostat doses to be investigated are:

- 3 mg weekly
- 5 mg weekly

In the Dose Confirmation Phase, 9 patients will receive entinostat at the prospective MTD/RP2D identified in the Dose Escalation Phase.

All patients will self-administer entinostat at the assigned dose and regimen PO. On study days on which patients receive both entinostat and pembrolizumab, entinostat is to be taken prior to pembrolizumab.

Pembrolizumab

The pembrolizumab treatment to be used in this study is outlined in Table 2-1.

Table 2-1 **Study Treatment**

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every three weeks (Q3W)	Intravenous (IV)	Day 1 of each cycle (3-week cycles)	Experimental

Pembrolizumab treatment will begin on C1D1. Pembrolizumab will be administered on D1 of each 3-week treatment cycle after all procedures and assessments have been completed as detailed on the Schedule of Study Assessments (Table 1-1 of the protocol or, for the EMIC cohort Table 1-2 of the protocol).

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

2.3.4 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 progressive disease as per irRECIST and RECIST 1.1, 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.

2.3.4.1 Tumor Measurement and Disease Response Assessment

Initial tumor imaging at screening must be performed within 28 days prior to C1D1. (Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality, have been performed within 28 days prior to C1D1, *and can be assessed by the central imaging vendor*). Patients will have radiological disease assessments performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during study treatment until progressive disease. If a patient comes off study for reasons other than progressive disease, radiological assessments will continue on this same study schedule until progressive disease is unequivocally documented. Tumor assessments should be kept to the calendar schedule and not be delayed for delays in cycles or study drug administration. Disease response in target and non-target lesions will be assessed locally by the Investigator using irRECIST and RECIST 1.1.

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
- 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.

2.3.4.2 Disease Response Assessment Criteria

Patients will have radiological disease assessments performed every 6 weeks (± 3 days) (i.e., Week 6, Week 12, etc.) until unequivocal PD or closure of the study by the Sponsor. All scans will be submitted electronically to a central core radiologic laboratory. Scans from patients who were determined by the Investigator to have a response to treatment (CR or PR) will be reviewed by the core radiologic laboratory to confirm response. Scans from non-responders may also be reviewed by the core radiologic laboratory at the direction of the Sponsor.

Disease response in target and non-target lesions will be assessed locally by the Investigator using immune response RECIST (irRECIST) and RECIST 1.1.

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.

When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix 3 of the protocol. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy and then experience subsequent disease response. This data will be captured in the clinical database.

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

2.3.5 Treatment After Initial Radiologic Progression

Immune-related RECIST will be utilized to account for the unique tumor response characteristics seen with pembrolizumab treatment. Immunotherapeutic agents such as pembrolizumab 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. 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 pembrolizumab and entinostat while waiting for confirmation of PD if they are clinically stable as defined by:

- Absence of signs and symptoms indicating clinically significant progression of disease;
- No decline in ECOG performance status;
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and

follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 3 of the protocol, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 13 of the protocol and submitted to the central imaging vendor.

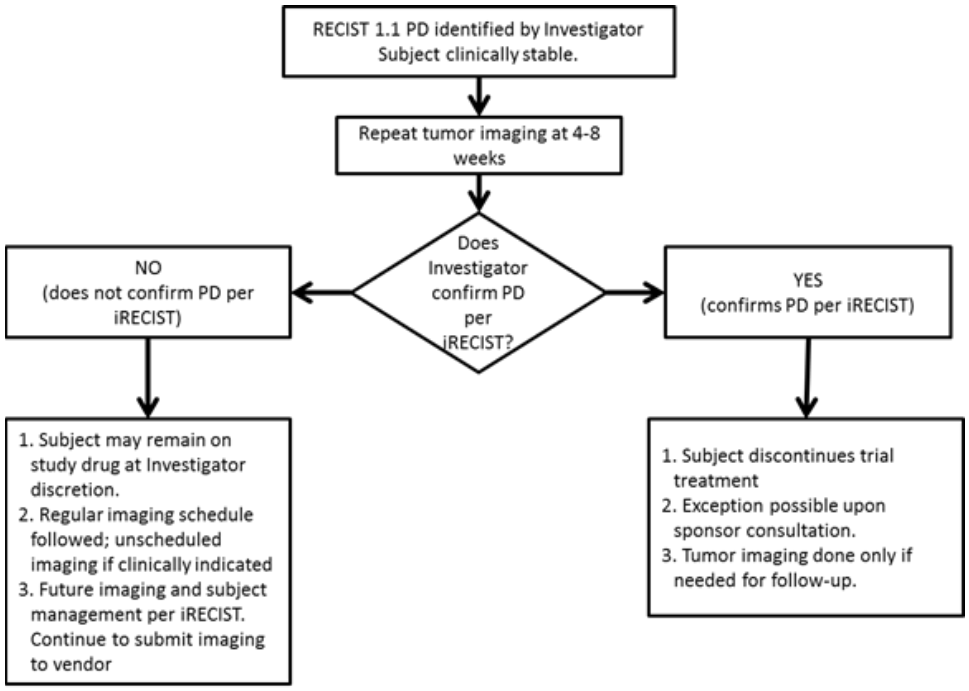
A description of the adaptations and iRECIST process is provided in Appendix 3, with additional details in the iRECIST publication (Seymour 2017). A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 2-2 and illustrated as a flowchart in Figure 2-2.

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

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

BICR = Blinded Independent Central Review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 2-2: Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator



NOTE: If a patient has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease), 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 intervals and be submitted to the central imaging vendor.

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

2.3.6 Protein Lysine Acetylation and Immune Correlates Assessments

Blood

Based on preclinical studies it is suggested that entinostat may specifically target a population of MDSCs and thus improve the response to PD-1 or PD-L1 antibody treatment. The Sponsor plans to evaluate populations of MDSC and other myeloid cells in peripheral blood and tumor tissues of the patients (if available) and also to evaluate the basic T-cell function in patients, with the expectation that if MDSC level is decreased the response to antigens would be improved.

Blood for immune correlates and protein lysine acetylation is to be shipped on the same day of draw to the applicable laboratories with proper advanced notification according to the laboratory manual.

Blood

For patients in the EMIC Cohort, blood for immune correlates is to be collected pre-dose on D-14, C1D1, C1D8, and C2D15. For patients in all other cohorts, blood for immune correlates is to be collected pre-dose on C1D1, C2D1, and C2D15. At these time points, 40 mL of heparinized peripheral blood is to be collected and shipped overnight to a central laboratory facility for analysis.

For patients in the EMIC Cohort, blood for protein lysine acetylation is to be collected pre-dose on D-14, C1D1, C1D15, and C2D15. For patients in all other cohorts, blood for protein lysine acetylation is to be collected pre-dose on C1D1, C1D15 and C2D15. At these time points, approximately 16mL of blood is to be collected and shipped overnight to a central laboratory facility for analysis.

The following immune correlate analyses will be performed on the collected samples:

Cell Phenotype:

- MDSC: Lin (CD3, CD14, CD19, CD56) negative, $HLA^{-}DR^{-}$, $CD33^{+}$;
- MDSC: $CD11b^{+}CD14\text{-}CD33^{+}$;

- PMN-MDSC: $CD11b^{+}CD14^{-}CD33^{+}CD15^{+}$;
- M-MDSC: $CD11b^{+}CD14^{-}CD33^{+}CD15^{-}$;
- M-MDSC: $CD14^{+}HLA\text{-}DR^{-}$/lo;
- Monocytes: $CD14^{+}CD16^{+}CD66b^{-}HLA^{-}DR^{+}$ including subsets of classical CD14hiCD16, intermediate CD14hi$CD16^{+}$ and non-classical $CD14^{+}$CD16hi;
- Dendritic cells: $Lin^{-}HLA^{-}DR^{+}CD303^{+}$ (BDCA2) plasmacytoid; $Lin^{-}HLA^{-}DR^{+}CD1c^{+}$ (BDCA1) myeloid; $Lin^{-}HLA^{-}DR^{+}CD141^{+}$ (BDCA3);
- Neutrophils: $CD11b^{+}CD14^{-}CD15^{+}$/$CD66b^{+}$ cells in high density fraction;
- T cells: $CD3^{+}CD4^{+}$; $CD3^{+}CD8^{+}$; Regulatory T cells: $CD4^{+}CD25^{+}FoxP3^{+}$;
- B cells: CD19.

Cell Function:

Mononuclear cells stimulated with CD3/CD28, ConA, and tetanus toxoid. Cell proliferation by ^{3}H-thymidine uptake will be measured. Supernatant will be collected and interleukin-2, IFN-γ, and GM-CSF will be measure by enzyme-linked immunosorbent assay.

Tumor Tissue

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

- During **screening** from **all** patients on a **mandatory** basis.
- On **C2D15 (+3 days)** on an **optional** basis from patients in **the Dose Escalation/Confirmation Phase**. All patients in the Dose Escalation/Confirmation Phase will be strongly encouraged to provide an optional biopsy in order to help understand dose-immune correlate effects.
- On **C2D15 (+3 days)** on a **mandatory** basis from the **first 10 patients (in total, across cohorts) in Stage 1 in the Expansion Phase, the first 10 patients in the EMIC Cohort, and the first 10 patients in the CRC Cohort.**
- If, based on an interim review of tumor tissue data from the initial patients in

the Expansion Phase, such data are considered informative, then tumor tissue samples will be collected on a mandatory basis from all subsequent patients in the Expansion Phase on C2D15 (+ 3 days). Alternatively, if such data are not considered informative, these samples will not be collected from subsequent patients.

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. If patients have only one measurable lesion per RECIST v1.1:

1. the biopsy specimen should be obtained from a non-target lesion
2. this lesion should not have been in a field of prior-irradiation unless confirmed progression of the lesion

Should a patient opt out of a mandatory biopsy procedure, it will be considered a protocol deviation; however, the patient will be allowed to continue treatment on study.

Tissue samples will be analyzed for changes in expression of checkpoint inhibitors (PD-1/PD-L1) Cohorts 1, 2, and 3 only) in tumor biopsies pre- and post-therapy as well as the following immune correlates:

- MDSC: $CD33^{+}S100A9^{+}$;
- Macrophages $CD163^{+}$ or $CD68^{+}$ cells;
- Neutrophils – Neutrophil $elastase^{+}$ cells;
- Dendritic cells – DC-SIGN (CD209);
- CD4, CD8, Granzyme B, and FoxP3 positive cells will be done as appropriate if the MDSC level in the tissues is decreased.

2.3.7 Pharmacokinetic Assessments

Entinostat

Blood samples will be collected to assess the PK of entinostat and will be quantified by a sensitive and specific validated bioanalytical method. One (1) blood samples will

be collected at the following time points:

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

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

Pembrolizumab

Samples for determination of trough pembrolizumab levels and anti-pembrolizumab antibodies will be collected at the following time points (all taken pre-dose):

- C1D1
- C2D1
- C4D1
- C6D1
- C8D1
- Every 4 cycles thereafter until last dose of pembrolizumab
- 30 days after the last pembrolizumab dose (or until the patient starts new anti-cancer therapy).

All pre-dose trough samples should be collected within 24 hours before the pembrolizumab infusion.

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

2.3.8 Safety Assessments

The following assessments will be performed to evaluate the safety profile of entinostat and pembrolizumab. 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, or Table 1-2 for EMIC Cohort).

- Vital signs: temperature, pulse rate, respiration 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, uric acid, thyroid-stimulating hormone (TSH), free thyroxine (FT4), and total or free triiodothyronine (T3 or FT3)
- In the CRC cohort, blood tumor marker CEA should be drawn on day 1 of each cycle.

2.3.9 Other Assessments

Other assessments include patient demographics, prior cancer history, prior systemic

anti-cancer therapy, prior surgery related to indicated cancer, prior radiation therapy, medical history, physical examinations, entinostat administration and accountability, pembrolizumab 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 3 mg dose cohort. For the expansion phase, tabulations will be provided by tumor type and overall. Data from dose determination phase for the patients who received 5 mg will be included in dose expansion phase.

All statistical analyses will be performed using SAS® Version 9.2 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 pembrolizumab). 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 tumor response and other efficacy-related endpoints in the Phase 2 portion of the study. The FAS is a subset of all enrolled patients, with patients excluded for the following reasons:

- Failure to receive at least one dose of entinostat and pembrolizumab
- Lack of baseline data for those analyses that require baseline data

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 data freeze for the primary analysis.

3.2.3 Evaluable Analysis Set

The Evaluable Analysis Set is a subset of the FAS. The Evaluable Analysis Set is defined as patients who had week 6 assessment or were removed from study for progression of disease (or suspected progression) or for adverse event that was attributed to study drug. Patients who were excluded from Evaluable Analysis Set included those who discontinued due to adverse events that were not related to study drug or withdrew consent from treatment or study before the Week 6 scan assessment.

3.2.4 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 pembrolizumab. 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.

3.2.5 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:

- ORR (CR or PR) by irRECIST and RECIST 1.1
- CBR (CR, PR, or SD for at least 24 weeks) by irRECIST and RECIST 1.1
- PFS at 6 months by irRECIST and RECIST 1.1
- PFS as determined by irRECIST and RECIST 1.1
- 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 pembrolizumab 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
- $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time zero to the last measurable concentration
- $AUC_{0\text{-}inf}$, 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 pembrolizumab
  - 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 pembrolizumab
  - 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

[redacted]

3.4 Disposition and Evaluability

3.4.1 Disposition

The number and percentage of patients who were enrolled, dosed, and withdrew prior to receiving a dose (including reasons for not completing dosing), the number of cycles on treatment, 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 tumor type and overall 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 tumor type for the Safety Analysis Set (Phase 2). 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 Cancer Disease History

The following baseline disease characteristics variables will be summarized (if available) **for each cohort in Phase 2** and the Safety Analysis Set:

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

Disease history, including prior anti-cancer therapies (e.g. PD-1/PD-L1), surgeries, and radiotherapy, will be summarized by dose cohort and by tumor type for the Safety Analysis Set (Phase 1 only) and for the Safety Analysis Set (Phase 2 only), respectively. Frequency statistics will be presented for ECOG performance status, primary tumor location, and disease status at enrollment. Summary statistics will be

presented for months 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 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 Safety Analysis Set (Phase 2).

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 tumor type (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 total number of cycles started and the total number of cycles started by category (≥1, ≥2, ≥3, so on) will be tabulated for each patient and summarized for each study phase. The 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 dose intensity = [total amount of actual dose of study drug / (prescribed dose per cycle*# of cycles)] * 100 will be calculated for all patients. Similar analyses will be performed for pembrolizumab 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. ORR will be estimated for each cohort evaluated in the Expansion Phase using irRECIST as the primary endpoint. Crude proportion of patients with best overall response of CR or PR, along with a 2-sided 95% CI, will be calculated for each cohort. The width of the CI will be adjusted to account for the multistage design (Atkinson, 1985). Additionally, a 90% one-sided CI of the form (π, 1] will be reported for cohort 1 and a 95% one-sided CI will be reported for cohort 4 since the sample size for the Expansion Phases for cohorts 1 and 4 were determined using a one-sided significance level of 10%, 5%, respectively.

Crude proportion of patients with best overall response of CR or PR, along with a 2-sided 92% CI will be calculated for cohorts 2 and 3. ORR based on RECIST 1.1 will be analyzed in a similar manner.

Clinical Benefit Rate

Clinical benefit rate, as determined by irRECIST, will be estimated based on the crude proportion of patients in each cohort whose best overall response during the course of study treatment is a irCR, irPR, or irSD lasting for at least 6 months. Stable disease based on irRECIST will be measured from the start date of study treatment until the criteria for irPD is first met. Approximate 2-sided 95% CIs will be calculated for each cohort. Clinical benefit rate, as determined by RECIST 1.1, will be estimated based on the crude proportion of patients in each cohort whose best response during the course of study treatment is a CR, PR, or SD lasting for at least 6 months. Stable disease based on RECIST 1.1 will be measured from the start date of study treatment until the criteria for PD is first met. Approximate 2-sided 95% CIs will be calculated for each cohort.

Progression-free Survival

The PFS, defined as the number of months from first dose date 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). The PFS at 6 months by irRECIST and RECIST 1.1 will be analyzed in a similar manner.

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 enrollment	Censored
No post-baseline assessment and no death	Date of enrollment	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

Overall Survival

Overall survival is defined as the number of months from first dose date 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 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.

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 3-2. 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 3-2. 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
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.

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 may be classified and summarized as chemotherapy, immunotherapy, radiation, surgery or other.

3.9 Subgroup Analyses

Supportive analyses will be performed to determine whether the estimated treatment effect that is observed for the ORR and PFS (based on irRECIST) 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 ORs (or hazard ratios) and 95% CIs across subgroups.

Subgroup analyses:

- PD-L1 expression (Yes, No, Missing)
- Current Visceral Involvement (Yes, No, Missing)
- Baseline LDH (%>ULN) (Yes, No, Missing)
- Previously treated with ipilimumab and PD-1 (Melanoma cohort only)
- Previously treated with BRAF/MEK Inhibitor (Melanoma cohort only)
- Baseline classical monocytes
- NLR = (ANC/ALC)
- dNLR = (ANC/(WBC-ANC))
- Smoking Status (Current Smoker, Former Smoker, Never a Smoker) (NSCLC Cohorts only)

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 18.0 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.

For Phase 1, AE relatedness criteria is defined as “definitely not related”, “probably not related”, “probably related” and “definitely related”.

A summary of AEs, including incidences of:

- AEs
- SAEs
- AEs related to entinostat (“not related”, “unlikely related”, “possibly related”

or "related" for Phase 2)
- AEs related to pembrolizumab ("not related", "unlikely related", "possibly related" or "related" for Phase 2)
- AEs related to any study drug
- SAEs related to entinostat, pembrolizumab, or both
- AEs leading to dose modification of entinostat, pembrolizumab, or both
- AEs leading to discontinuation of entinostat, pembrolizumab, 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, pembrolizumab, or both

will be presented by dose cohort in Phase 1 and by tumor type in Phase 2.

Incidences of all AEs will be presented by SOC and PT by dose cohort in Phase 1 and by tumor type 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, pembrolizumab, 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 tumor type.

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 (screening and EOT).

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 pembrolizumab and anti-pembrolizumab antibodies at each cycle and time point.

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

3.12 Immune Correlate 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. The Wilcoxon signed rank test (for within-treatment comparisons) and Wilcoxon rank sum test (for between-treatment comparisons) will be used to identify any systematic changes in biomarker levels from baseline. Additionally, the correlation among the various initial immune correlate values may be assessed by calculating Spearman's correlation coefficient. Analysis of covariance models may be used to explore the relationship between changes in immune correlates and selected measures of antineoplastic activity (e.g., maximum change from baseline in the sum of product diameters in measurable lesions).

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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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