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

Syndax Protocol SNDX-275-0601

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Investigator's Agreement

I have read the attached protocol entitled "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" dated 12 April 2018, and agree to abide by all provisions set forth therein.

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

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

- me
- my sub-investigators

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

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

_____
Signature

_____ _____
Name of Principal Investigator Date

1. PROTOCOL SYNOPSIS SNDX-275-0601

Title: 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

Study Phase: Phase 1b/2

Indication: Melanoma, Non-small Cell Lung Cancer (NSCLC), and Mismatch Repair-Proficient Colorectal Cancer"

Primary Objective:

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, NSCLC, and mismatch repair-proficient colorectal cancer as determined by overall response rate (ORR), per the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in each cohort evaluated.

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 irRECIST criterion, including:

- Clinical benefit rate (CBR) (i.e., 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), laboratory parameters, and electrocardiograms (ECGs).

Exploratory Objectives:

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

[redacted]

Hypothesis:

Entinostat has been shown in preclinical models to reduce the number and inhibit the function of host immune suppressor cells in order to enhance the anti-tumor activity of immune checkpoint blockade. It is hypothesized that entinostat combined with pembrolizumab will result in an improved response rate for the combination compared to either agent alone. Preclinical study data suggest that entinostat specifically targets MDSCs and thus would improve the response to PD-1/PD-L1-blocking antibody (i.e., pembrolizumab) treatment. The Sponsor accordingly proposes to evaluate populations of MDSCs and other myeloid cells in peripheral blood and tumor tissues as well as basic T-cell function in patients, with the expectation that if the MDSC level is decreased, the response to antigens would be improved.

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, 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 cohorts 1 and 4. For cohorts 2 and 3, the single proportion binomial test statistic is used to test for statistical significance. 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.

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 into the study within 3 days of starting study treatment. With the exception of those in the EMIC cohort, patients will receive entinostat in combination with pembrolizumab on Cycle 1, Day 1 (C1D1), within 3 days from enrolling into the study.

A total of 15 patients will be enrolled in an EMIC Cohort. EMIC patients will be enrolled in the study within 3 days of starting study treatment on Day -14 (initiation of entinostat monotherapy) and will participate in a 2-week entinostat monotherapy period. The purpose of this 14-day lead-in phase is to obtain pre-and post-entinostat monotherapy correlative data in blood and tissue. After completion of the 2-week entinostat monotherapy period, patients in the EMIC Cohort will start entinostat in combination with pembrolizumab on C1D1. Patients in the EMIC Cohort will receive entinostat beginning at 5mg weekly for the monotherapy period, and then will receive entinostat in combination with pembrolizumab at the RP2D as identified in the Phase 1b Dose Escalation/Confirmation portion of the study.

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.

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

Blood for immune correlates is to be collected from patients in the EMIC Cohort pre-dose on D-14, C1D1, C1D8, and C2D15. In all other cohorts, blood for immune correlates is to be collected pre-dose on C1D1, C2D1, and C2D15. Blood for protein lysine acetylation and for entinostat and pembrolizumab PK assessments will be collected according to the Schedule of Events.

Patients will have radiological disease assessments performed during screening and every 6 weeks (+/-3 days) (Week 6, Week 12, etc.). 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 primarily using irRECIST.

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

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

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 (F/U) visits 30 days and 90 days thereafter. After completion of the 30-day Safety 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.

Phase 1b (Dose Escalation/Confirmation): The Dose Escalation/Confirmation Phase of the study, in which patients with NSCLC will be enrolled, employs a classical 3+3 design, with the determination of DLT and the MTD and/or RP2D based on entinostat in combination with pembrolizumab in C1.

Although decisions regarding dose escalation will be made primarily based on review of data from C1, safety data will also be collected from all patients continuing treatment and these data will be reviewed in an ongoing manner by the Sponsor Study Physician(s) including Medical Monitor, in consultation with the Investigators. Any detected cumulative toxicity may require later dose reductions and/or other changes to the dosing schedule, as appropriate, including further refinement of the RP2D.

Dose Escalation: The initial 3-6 patients will receive entinostat at a starting dose of 3mg on D1, D8, and D15 along with pembrolizumab 200 mg via intravenous (IV) infusion on D1 of a 21-day cycle. Assuming an acceptable safety profile, escalation to an entinostat dose of 5mg weekly is planned, keeping the pembrolizumab dose constant. However, based on evaluation of the safety and tolerability data of the previous dose level, it may also be decided that accrual will take place at an intermediate dose level or alternate dosing schedule. Toxicities will be assessed by the Investigator using the United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. The decision regarding whether to proceed to the next dose level will be made by the Sponsor Study Physician(s) in consultation with the Investigators after the majority of the safety assessments for each cohort are completed.

All patients within a cohort are to complete C1, have safety assessments performed through C2D1, and be assessed for DLT before enrollment of the next cohort may commence. If <33% patients within a cohort have a DLT (i.e., <2 of up to 6), then enrollment of the next cohort may commence with approval from the Sponsor Study Physician(s) in consultation with the Investigators. If ≥33% (≥2 of up to 6) of patients within a cohort experience a DLT, then the DLT dose level will have been reached.

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

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

Six patients will need to be treated in a dose level for that dose to be considered for the Dose Confirmation stage. The recommended dose for Phase 2 investigation will be the higher of either 3 or 5mg weekly by mouth (PO) that results in less than a 33% incidence of DLT. The final determination of the optimal RP2D will consider both acute and cumulative toxicities; the incidence of required dose delays, reductions, and discontinuations; and the overall facility of administration in clinical practice.

Dose Confirmation: The prospective MTD/RP2D identified in the Dose Escalation Phase will be confirmed in 9 patients in the Dose Confirmation Cohort, to obtain additional AE, immune correlate, and anti-tumor activity data on entinostat in combination with pembrolizumab.

The decision regarding the RP2D will be made by the Sponsor Study Physician(s), based on a review of all data obtained from both the Dose Escalation and Confirmation Phases, with input from the Investigators.

After completion of the Dose Escalation/Confirmation Phase of the study, with identification of the MTD/RP2D, the Phase 2 portion of the study will commence.

Phase 2 (Expansion): In the Expansion Phase, entinostat in combination with pembrolizumab will be evaluated using the RP2D identified in the Dose Escalation/Confirmation Phase. Up to 4 Expansion Cohorts consisting of distinct subsets of patients with solid tumor cancers may be explored. Expansion cohorts 1 and 4 evaluated during the Expansion Phase will employ a Simon 2 stage design. Expansion cohorts 2 and 3 will employ single proportion binomial test (See **Sample Size Considerations**). The final decision about which Expansion Cohorts to study will be based on data from the Dose Escalation/Confirmation Phase, emerging clinical data from other studies, and/or nonclinical data. Expansion cohorts may include:

1. Cohort 1: NSCLC, with squamous cell or adenocarcinoma histology who have not been treated with a PD-1 or PD-L1blocking antibody
2. Cohort 2: Patients with NSCLC (any histology) who have previously been treated with and unequivocally progressed on either a PD-1 or PD-L1-blocking antibody
3. Cohort 3: Patients with melanoma who have previously been treated with and unequivocally progressed on either a PD-1 or PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A])
4. Cohort 4: Patients with CRC (mismatch repair-proficient) who have not been previously treated with a PD-1 or PD-L1 blocking antibody

EMIC Cohort:

After completion of Stage 1 of Cohort 1 in the Expansion Phase, provided the criteria for continuation are met (i.e., at least 3 of 13 patients in Stage 1 experience a CR or PR; see **Sample Size Considerations**), 15 patients with NSCLC (either squamous cell adenocarcinoma or mixed histology) will be enrolled in an EMIC Cohort. Patients will be randomly assigned to Stage 2 of Cohort 1 or the EMIC Cohort on a 1:1 basis until the EMIC Cohort is fully enrolled. As stated previously, EMIC patients will participate in a 2-week entinostat monotherapy period prior to starting entinostat in combination with pembrolizumab. The purpose of this 14-day lead-in phase is to obtain pre-and post-entinostat monotherapy correlative data in blood and tissue.

Sample Size Considerations:

Dose Escalation/Confirmation 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%) or to confirm a dose for the Confirmation Phase - is 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.

As stated previously, a total of 9 additional patients will be enrolled at the potential RP2D in the Dose Confirmation Cohort to obtain additional AE, immune correlate, and anti-tumor activity data on entinostat at the MTD or other dose recommended for further investigation in Phase 2 (i.e., RP2D) in combination.

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 cohort 1, 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 optimum version of Simon's 2-stage design, with 90% power and 1-sided significance level of 5%. For cohorts 2 and 3, the number of responders needed to declare the study a success was based on single proportion binominal test with 90% power and 1-sided significance level of 5%. Note that the protocol may be amended to allow for enrollment of additional or different cohorts, for example, patients with PD-L1-positive NSCLC, based on emerging data during study conduct.

Syndax will conduct one administrative analysis when at least 60% (42 out of 70 patients in cohort 2, 31 out of 52 patients in cohort 3) of patient information have accrued in cohorts 2 and 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 to spend for the first administrative look and leaving 0.04 alpha for the final analysis.

Cohort 1 (NSCLC patients with squamous cell and adenocarcinoma histology not 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 for both tumor types. 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 70 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, the single proportion (or one sample) binomial test will be used. Ninety-six percent 1-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 have 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 to spend for the first administrative look and 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 52 patients will be enrolled in Cohort 3. A true ORR of 25% is hypothesized. An ORR 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, , the single proportion (or one sample) binomial test will be used. Ninety-six percent 1-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 have 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 to spend for the first administrative look and 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 design elements specified above, up to 37 patients may be enrolled during the first stage: if less than or equal to 2patients 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 out 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%.

Endpoints

Primary Efficacy Endpoint

- ORR, as determined by the local investigator using irRECIST

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

- CBR (CR+PR+SD) at 6 months
- PFS status at 6 months
- PFS
- OS

In patients who experience a response to treatment (CR or PR):

- DOR
- TTR

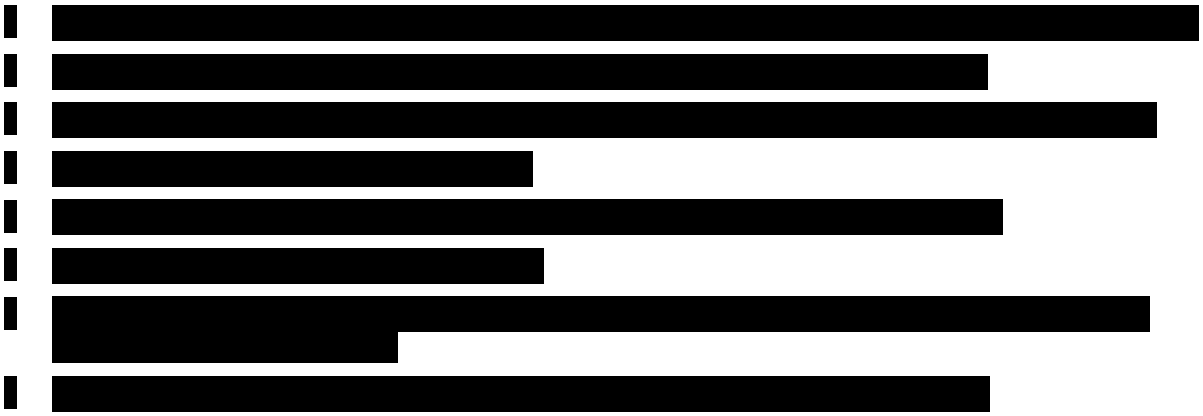
An analysis of efficacy endpoints also will be performed, with response determined using RECIST, version 1.1 and irRECIST.

Safety:

- Incidence of treatment-emergent AEs, SAEs, AEs resulting in the permanent discontinuation of study drug, and deaths occurring within 90-days of last dose of study drug
- Changes from baseline in laboratory, vital signs and ECG results

Exploratory:

[redacted]



Summary of Patient Eligibility Criteria:

INCLUSION CRITERIA

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

Patients with NSCLC

1. Has histologically- or pathologically-confirmed recurrent or metastatic NSCLC.
2. If has adenocarcinoma, required to have previously been tested for anaplastic lymphoma kinase (ALK) rearrangements and epidermal growth factor receptor (EGFR) (Exon 19 Deletion and Exon 21 L8585R Substitution) mutations, with results available for collection in this study, and, if positive, has been treated with prior EGFR or ALK therapy.
3. Received at least 1 chemotherapeutic regimen in the advanced/metastatic setting and experienced documented, unequivocal progressive disease by either RECIST 1.1 or clinical assessment. In addition:
    - If patient has EGFR mutation-positive or ALK translation-positive disease, must have received an EGFR inhibitor or ALK inhibitor, respectively, in addition to the above chemotherapy regimen.
    - Patients who received adjuvant or neoadjuvant platinum-based doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible; in such cases, the adjuvant or neoadjuvant platinum-based doublet chemotherapy regimen will count as a line of therapy.
    - Patients with recurrent disease >6 months after adjuvant or neoadjuvant platinum-based doublet chemotherapy who subsequently experienced PD during or after a platinum-based doublet chemotherapy regimen given to treat the recurrences, are eligible; the second platinum-based doublet chemotherapy regimen does not count as another line of therapy.
    - Patients who received pemetrexed, bevacizumab, or erlotinib as maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and subsequently progressed after maintenance therapy) are eligible; such therapy does not count as a line of therapy. However, if the patient received a tyrosine kinase inhibitor (TKI) after failure of platinum-based doublet chemotherapy, the TKI will count as an additional line of therapy.
4. Patients with NSCLC enrolled in Cohort 1 of the Expansion Phase should not have been previously treated with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A])

Patients in Expansion Phase, Cohorts 2 (NSCLC) and 3 (Melanoma)

5. Previously treated with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A]) and experienced documented, unequivocal radiographic progression of disease by irRECIST, or similar criteria during or within 12 weeks after last dose of such treatment. Patients must have received at least 6 weeks of PD-1/PD-L1 therapy for Cohort 2 and at least 8 weeks of PD-1/PD-L1 therapy for Cohort 3. For patients who received such agents in a clinical trial, documentation of progressive disease

requires a confirmatory scan. For patients who had been treated with such agents outside of a clinical trial, documentation of progressive disease will be based on both radiographic and clinical assessment. If the requirement for a confirmatory scan is deemed not to be in the patient's best interests based upon his/her overall condition, including performance status and clinical symptoms, this requirement may be waived in consultation with the Sponsor's Medical Monitor; however, patients who have not had a confirmatory scan because of rapid progression and clinical deterioration should not be enrolled onto this trial. In all cases, the scan obtained during the screening process may serve as the confirmatory scan.

(Note: Patients who are currently receiving pembrolizumab and have clear, unequivocal evidence of PD may be eligible. Such patients are to be discussed with the Sponsor Study Physician on a case-by-case basis prior to enrollment of the patient in the study.)

Patients with Melanoma

6. In addition to having been previously treated with a PD-1/PD-L1-blocking antibody (inclusion #5), has a histologically- or cytologically-confirmed diagnosis of unresectable or metastatic melanoma and experienced unequivocal progressive disease during treatment with a BRAF inhibitor if BRAF V600 mutation-positive. Treatment with BRAF inhibitor may occur AFTER treatment with the checkpoint inhibitor.

Patients in Expansion Phase, Cohort 4 (Colorectal Cancer)

7. Received at least 1 chemotherapeutic regimen in the advanced/metastatic setting and experienced documented, unequivocal progressive disease by either RECIST 1.1 or clinical assessment. Must have documented mismatch repair-proficient colon cancer as determined by either immunohistochemistry for mismatch repair proteins or PCR-based functional microsatellite instability. Patients with colorectal cancer enrolled in Cohort 4 should not have been previously treated with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI36MEDI4736, or GNE PDL1 [MPDL3280A])

All Patients

8. Aged 18 years or older on the day written informed consent is given.
9. If has brain metastases, must have stable neurologic status following local therapy (surgery or radiation) for at least 4 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent), and must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs. (Patients with a history of carcinomatous meningitis are not eligible.)
10. Evidence of locally recurrent or metastatic disease based on imaging studies (e.g., CT, MRI) within 28 days before the first study drug dose:
    - At least 1 measurable lesion ≥20 mm by conventional techniques or ≥10 mm by spiral CT scan or MRI, with the last imaging performed within 28 days before the first study drug dose. If there is only 1 measurable lesion and it is located in previously irradiated field, it must have demonstrated unequivocal progression according to RECIST, version 1.1.
11. If receiving radiation therapy, has had a 2-week washout period following completion of the treatment prior to receiving the first study drug dose and continues to have at least 1 measurable lesion, per above criterion.
12. ECOG performance status of 0 or 1.

13. Has the following laboratory parameters:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1.5\times10^9$/L
Platelets	$\geq 100\times10^9$/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[1] creatinine clearance (CrCl) (glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5× the upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels >1.5× institutional ULN
Hepatic	
Total bilirubin	≤1.5×ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5×ULN
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5×ULN **OR** ≤5×ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

14. Female patients of childbearing potential must have a negative serum pregnancy test during screening and a negative urine pregnancy test within 72 hours prior to taking first dose of study drug. If a patient is of childbearing potential, the patient must agree to use effective contraception, as defined in the protocol (Section 8.5.3), during the study and for 120 days after the last dose of study drug. Non-childbearing potential is defined as (by other than medical reasons):
    - ≥45 years of age and has not had menses for >2 years,
    - Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation.
    - Post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study drug. Please see Section 8.5.3, Contraception, for a list of acceptable birth control methods.
15. If male, agrees to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug. Please see Section 8.5.3, Contraception, for a list of acceptable birth control methods.
16. Experienced resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If patient underwent major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
17. Willing to have fresh tumor samples collected during screening and at other time points designated as mandatory, per the Schedule of Study Assessments. 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.

18. Able to understand and give written informed consent and comply with study procedures.

EXCLUSION CRITERIA

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

1. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
2. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
3. History of interstitial lung disease (ILD).
4. Allergy to benzamide or inactive components of entinostat.
5. History of allergies to any active or inactive ingredients of pembrolizumab or severe hypersensitivity (>= Grade 3) to pembrolizumab.
6. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator, including, but not limited to:
    - Myocardial infarction or arterial thromboembolic events within 6 months prior to baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QTc interval > 470 msec.
    - Uncontrolled heart failure or hypertension, uncontrolled diabetes mellitus, or uncontrolled systemic infection.
    - Another known additional malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma, squamous cell of the skin, cervical intraepithelial neoplasia [CIN]/cervical carcinoma *in situ* or melanoma *in situ* or ductal carcinoma *in situ* of the breast). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years.
    - Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
    - Active infection requiring systemic therapy.
    - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

      Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 2 weeks prior to the first dose of study drug or are on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent). This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
7. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
8. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
9. Received a live virus vaccination within 30 days of the first dose of treatment.
10. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to baseline or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

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

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

    Note: If patient underwent major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

12. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to the first dose of treatment.
13. Currently receiving treatment with any other agent listed on the prohibited medication list in Section 8.5.1 such as valproic acid, or other systemic cancer agents within 14 days of the first dose of treatment.
14. If female, is pregnant, breastfeeding, or expecting to conceive, or if male, expect to father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study drug.
15. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
16. Known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative]).
17. For CRC expansion cohort, prior history of malignant bowel obstruction requiring hospitalization in the 6 months prior to enrollment
18. For the CRC expansion cohort, history of uncontrolled ascites, defined as symptomatic ascites and/or repeated paracenteses for symptom control in the past 3 months

Investigational Product:

Entinostat

Entinostat is a synthetic small molecule bearing the chemical name 3-pyridylmethyl-N-{4-[(2-aminophenyl)carbonyl] benzyl}carbamate and the molecular formula $C_{21}H_{20}N_4O_3$, with a molecular weight of 376.41. Entinostat is classified as an antineoplastic agent, specifically functioning as an inhibitor of histone deacetylases and therefore promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes that leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis. Entinostat is supplied in two strengths of film-coated tablets containing 1 mg (pink to light red) or 5 mg (yellow) of active ingredient.

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and programmed death ligand-2 (PD-L2). Pembrolizumab is an immunoglobulin G4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Pembrolizumab will be supplied as 50mg lyophilized powder for injection or 100mg/4 mL solution for injection.

Statistical Considerations:

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

Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

Treatment-emergent AEs reported during the study will be tabulated and listed by Medical Dictionary for Regulatory Activities (MedDRA version 18.0) System Organ Class (SOC) and Preferred Term (PT). Tables will display number and percentage of patients experiencing the event for the following categories: all AEs; AEs considered related to study drug; AEs by severity; DLTs; AEs occasioning treatment delay or discontinuation; and serious adverse events (SAEs). For the Dose Escalation/Confirmation Phase, the observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experienced DLT with a 2-sided 95% exact binomial confidence interval (CI).

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: baseline value, minimum and maximum post-baseline values, average post-baseline value, and last post-baseline value. Standard shift tables will also be prepared presenting worst post-baseline toxicity grade versus baseline. Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values. The Wilcoxon signed rank test may be used to assist in the identification of any systematic changes.

Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set.

ORR will be estimated for each cohort evaluated in the Expansion Phase, assessed using irRECIST. Crude proportion of patients with best overall response of CR or PR, along with a 2-sided 95% CI, will be calculated. 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 $(\pi_L, 1]$ will be reported since the sample size for the Expansion Phase was determined using a one-sided significance level of 10%. CBR at 6 months will be analyzed in a similar manner.

DOR will be calculated for patients who achieve a CR or PR and is defined as the number of months from the start date of the response (and subsequently confirmed) to the first date that recurrent disease or PD is documented. PFS is defined as the number of months from the date of the first dose of study drug to the earliest of documented PD or death due to any cause without prior progression. OS is defined as the number of months from the first dose of study drug to the date of death due to any cause. DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up. PFS rate at 6 months and corresponding 95% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

Procedures: The Schedule of Study Assessments for patients in the EMIC Cohort is included in Table 1-2. The Schedule of Study Assessments for all other patients is included in Table 1-1.

Table 1-1 Schedule of Study Assessments

Procedure	Screening (D -21 to -1)	Combination Therapy						EOT[1]	Safety F/U[2,3]	Post-Study F/U
		C1			C2		≥C3			
		D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
Provision of written informed consent	X									
Demographics	X									
Height	X									
Medical history, including underlying disease history	X									
Complete physical examination	X[4]	X[4]						X	X	
Symptom-directed physical examination		X	X	X	X	X	X			
ECG	X						X[5]	X		
Vital signs and weight	X	X			X		X	X	X	
ECOG performance status	X	X			X		X	X	X	
Radiological Imaging	X[6]						X[7]	X[8]		
Disease Response Assessment		X					X	X[9]		
Thyroid function tests	X[10]				X[10]		X[10]	X		
Pregnancy testing	X	X[11]								
Hematology, coagulation studies[12], and clinical chemistries[13]	X	X[14]	X	X	X	X	X	X		
Blood sample for immune correlates		X			X	X[15]				
Blood sample for protein lysine acetylation		X		X		X				
Tissue sample collection for immune correlates	X[16]					X[16]				
Entinostat self-administration		Entinostat is to be self-administered by the patient weekly), starting on C1D1								

Procedure	Screening (D -21 to -1)	Combination Therapy						EOT[1]	Safety F/U[2,3]	Post-Study F/U
		C1			C2		≥C3			
		D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
Pembrolizumab administration		X			X	\	X			
Blood sample for entinostat pharmacokinetics[17]		X	X	X	X					
Blood sample for pembrolizumab pharmacokinetics and anti-drug antibodies[18]		X			X		X		X	
Blood sample for tumor markers[19]		X			X		X	X		
Pre-treatment/concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	
Study drug compliance assessment		X	X	X				X		
Post-study treatment patient contact[20]									X	

[1] *The EOT visit is to be conducted within 7 days of study drug discontinuation.*

[2] *The first Safety F/U visit is 30 days after the EOT visit. After completion of the Safety F/U visit, patients who have not experienced PD are to be followed every 2 months until PD and 3 months thereafter until death or closure of the study by the Sponsor.*

[3] *The second Safety F/U visit is 90 days after the EOT visit.*

[4] *If the screening physical examination was performed within 7 days before baseline (C1D1), then a symptom-directed examination may be performed at baseline.*

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

[6] *Performed only if last scan was performed >28 days previously.*

[7] *Patients will have radiological disease assessments performed during screening and every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment.*

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

[9] *Disease assessments are to be performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment.*

[10] *In addition to screening, thyroid function tests (thyroid-stimulating hormone [TSH, thyrotropin], free thyroxine [T4], and triiodothyronine [T3] or free triiodothyronine [FT3]) are to be performed every 6 weeks during treatment starting at C2.*

[11] *For female patients of child-bearing potential, a serum pregnancy test is to be performed during screening and a urine pregnancy test is to be performed within 72 hours prior to taking the first study drug dose. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.*

[12] *Analytes tested include white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and, at screening only, prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT). Note: it is advisable to monitor PT and INR more frequently for patients who receive coumarin derivatives concurrently with entinostat.*

[13] *Analytes tested include ALT, AST, albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, sodium, potassium, chloride, bicarbonate, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, and uric acid. Magnesium is to be measured at baseline only, unless clinically indicated.*

[14] *Performed only if screening laboratory tests performed >7 days prior to C1D1 (baseline).*

[15] *Pre-dose on C1D1, C2D1 and C2D15 only.*

[16] *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****; and on* ***C2D15 (+3 days)*** *on a* ***mandatory*** *basis from the* ***first 25 patients (in total, across cohorts) in Stage 1 in the Expansion Phase****. 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.*

[17] *Blood samples for entinostat PK will be collected pre-dose on C1D1 as well as 2-4 hours post-dose on C1D1; on C1D8 (anytime post-dose), on C1D15 (anytime post-dose), and pre-dose on C2D1. The date and time of entinostat administration, the start time and stop time of the pembrolizumab infusion, and the date and time of PK sample collection must be recorded in the eCRF.*

[18] *Samples for pembrolizumab PK and anti-pembrolizumab antibodies will be collected pre-dose on C1D1, C2D1, C4D1, C6D1, C8D1 and every 4 cycles thereafter, and at 30 days after the last pembrolizumab dose (or until the patient starts new anti-cancer therapy).*

[19] *CEA in CRC cohort only*

[20] *Information regarding PD, alternate treatments, and survival status collected until study closure; every 2 months until PD, and then every 3 months thereafter.*

Table 1-2 Schedule of Study Assessments: EMIC Cohort

Procedure	Screening (D -35 to -15)	Mono-therapy Period	Combination Therapy Period						EOT[1]	Safety F/U[2,3]	Post-Study F/U
			C1			C2		≥C3			
		D -14	D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
Provision of written informed consent	X										
Demographics	X										
Height	X										
Medical history, including underlying disease history	X										
Complete physical examination	X[4]	X[4]							X	X	
Symptom-directed physical examination			X	X	X	X	X	X			
ECG	X							X[5]	X		
Vital signs and weight	X	X	X			X		X	X	X	
ECOG performance status	X	X	X			X		X	X	X	
Radiological Imaging	X[6]							X[7]	X[8]		
Disease Response Assessment		X						X	X[9]		
Thyroid function tests	X[10]					X[10]		X[10]	X		
Pregnancy testing	X	X[11]									
Hematology, coagulation studies[12], and clinical chemistries[13]	X	X[14]	X	X	X	X	X	X	X		
Blood sample for immune correlates		X	X	X			X				
Blood sample for protein lysine acetylation		X	X		X		X				
Tissue sample collection for immune correlates	X[15]						X[15]				

Procedure	Screening (D -35 to -15)	Mono-therapy Period	Combination Therapy Period						EOT[1]	Safety F/U[2,3]	Post-Study F/U
			C1			C2		≥C3			
		D -14	D1	D8	D15	D1	D15	Day 1			
Visit Window	-	-	-	±1D	±1D	±3D	±3D	±3D	±3D	±3D	±5D
Entinostat self-administration		Entinostat is to be self-administered by the patient weekly, starting on D-14									
Pembrolizumab administration			X			X		X			
Pre-treatment/concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	
Study drug compliance assessment		X	X	X	X				X		
Post-study treatment patient contact[16]										X	

[1] *The EOT visit is to be conducted within 7 days of study drug discontinuation.*

[2] *The first Safety F/U visit is 30 days after the EOT visit. After completion of the Safety F/U visit, patients who have not experienced PD are to be followed every 2 months until PD and 3 months thereafter until death or closure of the study by the Sponsor.*

[3] *The second Safety F/U visit is 90 days after the EOT visit.*

[4] *If the screening physical examination was performed within 7 days before the Day -14 visit, then a symptom-directed examination may be performed on Day -14.*

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

[6] *Performed only if last scan was performed >28 days previously.*

[7] *Patients will have radiological disease assessments performed during screening and every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment.*

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

[9] *Disease assessments are to be performed every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment.*

[10] *In addition to screening, thyroid function tests (thyroid-stimulating hormone [TSH, thyrotropin], free thyroxine [T4], and triiodothyronine [T3] or free triiodothyronine [FT3]) are to be performed every 6 weeks during treatment starting at C2.*

[11] *For female patients of child-bearing potential, a serum pregnancy test is to be performed during screening and a urine pregnancy test is to be performed within 72 hours prior to taking the first study drug dose. Pregnancy testing is to be repeated during the study any time pregnancy is suspected*

[12] *Analytes tested include white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and, at screening only, prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT). Note: it is advisable to monitor PT and INR more frequently for patients who receive coumarin derivatives concurrently with entinostat.*

[13] *Analytes tested include ALT, AST, albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, sodium, potassium, chloride, bicarbonate, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, and uric acid. Magnesium is to be measured at baseline only, unless clinically indicated.*

[14] *Performed only if screening laboratory tests performed >7 days prior to Day -14.*

[15] *Fresh tumor tissue samples are to be collected on a mandatory basis from the first 10 patients in the EMIC Cohort during screening and on C2D15 (+3 days).*

[16] *Information regarding PD, alternate treatments, and survival status collected until study closure; every 2 months until PD and then every 3 months thereafter.*

Study Glossary

Abbreviation/Acronym	Definition
ADaM	Analysis Dataset Model
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AZA	5-Azacitadine
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CBR	Clinical benefit rate
CEA	Cancer Embryonic Antigen
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRC	Colorectal cancer
CSC	Cancer stem cell
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation/Acronym	Definition
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
D	Day
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
F/U	Follow-up
FAS	Full Analysis Set
FDG	18F-deoxyglucose
FoxP3	Forkhead box P3
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage-colony stimulating factor
G-MDSCs	Granulocytic myeloid-derived suppressor cells
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus

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

Abbreviation/Acronym	Definition
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	By mouth
PP	Per-protocol
PR	Partial response
PT	Prothrombin time
Q2W	Every other week (i.e., every 2 weeks)
Q3W	Every 3 weeks
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SC	Subcutaneous(ly)
SDTM	Study Data Tabulation Model
SEER	Surveillance, Epidemiology, and End Results
SOC	System organ class
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event

Abbreviation/Acronym	Definition
TGF	Transforming growth factor
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
V-type	Variable-type
WBC	White blood cell (count)

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2. OBJECTIVES

2.1 Primary

The primary study objectives are:

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.

2.2 Secondary

Secondary study objectives are:

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 parameters.

2.3 Exploratory

[redacted]

3. ENDPOINTS

3.1 Efficacy

The primary efficacy endpoint is:

- ORR, as determined by irRECIST

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

- 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

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

3.2 Safety

Safety endpoints are:

- Incidence, severity and duration of treatment-emergent AEs, SAEs, AEs resulting in the permanent discontinuation of study drug, and deaths occurring within 90-days of last dose of study drug
- Changes from baseline in laboratory, vital signs, and ECG results

3.3 Exploratory

[redacted]

[redacted]

4. BACKGROUND AND RATIONALE

Despite recent advances in therapy, metastatic NSCLC, melanoma, and CRC represent oncologic indications with a significant unmet medical need, with affected patients having a poor prognosis.

Lung cancer is the leading cause of cancer death in the United States (US) (SEER 2014). The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program estimate for the number of new lung cancer cases in 2014 was approximately 224,210, with 159,260 deaths due to the disease that year (SEER 2014). The prognosis for patients with metastatic lung cancer is poor, with a low 5-year survival rate of 4% (Howlader 2014). NSCLC constitutes approximately 80% of all lung cancers, and it is estimated that 40% of patients with NSCLC present with metastatic disease. Cytotoxic chemotherapy and tyrosine kinase inhibitors have been shown to improve survival and quality of life in patients with metastatic NSCLC; however, OS remains poor and more effective therapies are urgently needed.

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive form of skin cancer. In contrast to other types of cancer, the incidence of melanoma has increased over the past several decades, with the incidence doubling every 10 years. The NCI, SEER Program, estimate for the number of new melanoma cases in 2014 was 76,100, representing 4.6% of all new cancer cases, with an estimated 9,710 deaths due to the disease that year (SEER 2014). Overall, the 5-year survival rate for melanoma, regardless of disease stage, is high (91%); however, for patients who present with metastatic disease and receive systemic treatment, the 5-year survival rate is considerably lower at 16% (SEER 2014).

Melanoma is considered to be one of the most immunogenic tumor types, due to the presence of tumor infiltrating lymphocytes in resected melanoma, occasional spontaneous regressions, and clinical responses to immune stimulation (Finn 2012). Although historically not considered to be an immunoresponsive tumor type, nonclinical and clinical evidence now supports the investigation of immunologic approaches for the treatment of NSCLC (Harvey 2014).

CRC is the second leading cause of cancer death in the United States with greater than 40,000 deaths each year. Median survival at the time of diagnosis has been extended with recent advances to approximately 30 months, but longterm survival remains dismal with 5-year overall survival at <10%. Immune checkpoint inhibitors have shown dramatic effect in a subset of patients with mismatch repair-deficient tumors (Le 2015), but this represents 3-5% of advanced CRC. In the remaining patients, immune

checkpoint inhibitors have been completely unsuccessful. Accordingly, there is great interest in combining immune checkpoint inhibitors with other classes of agents to induce immunosensitivity. Kim et al. demonstated entinostat therapy of immunocompetent CRC models resulting in sensitivity to immune checkpoint inhibition and commesurate decrease in MDSCs.

Several regulatory mechanisms in the immune system that are exploited by cancer have been identified, including regulatory T cells, MDSCs, tumor-associated macrophages and neutrophils, immune checkpoint pathways, and immunosuppressive cytokines (Kim 2014). Recent clinical studies with immune checkpoint inhibitory PD-1, PD-L1, and anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies have demonstrated highly promising responses in a number of tumor types, including both NSCLC and melanoma (Harvey 2014). Expression of the PD-1 ligand PD-L1 has been detected in lung, ovary, renal, and colon carcinomas and in malignant melanoma, but not in normal tissues, including the lung, uterus, kidney, colon, or skin (Harvey 2014). Abnormal expression of PD-L1 has been reported in 19% up to 100% of NSCLC tumors, with the variation in results dependent on the antibody, histology, and technique reported (Creelan 2014).

A number of immune checkpoint inhibitors are under clinical development for the treatment of solid tumors (Harvey 2014). Pembrolizumab (Keytruda®), a human monoclonal antibody against the PD-1 protein, represents the first anti-PD-1 therapy to receive regulatory approval in the US (Poole 2014). Pembrolizumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab is also indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda®. (Refer to Section 4.1.2 for detailed information regarding pembrolizumab.)

Nivolumab is another checkpoint inhibitor that targets PD-1. It is approved for the treatment of unresectable or metastatic melanoma in patients who experience disease progression following ipilimumab, and if BRAF V600 mutation positive, a BRAF inhibitor; and the treatment of metastatic squamous NSCLC in patients who experience disease progression after platinum-based chemotherapy.

In addition to pembrolizumab and nivolumab, there are other investigational immune checkpoint inhibitors targeting PD-1 or PD-L1, including MPDL3280A and MEDI-4736, which have also demonstrated efficacy in clinical studies in NSCLC. In particular, the anti-PD-1/PD-L1 therapies administered as single agent therapy in chemotherapy refractory patients have produced ORRs ranging

from 15 to 25%, the majority of which were rapid and ongoing 1 year after starting therapy (American Association for Cancer Research 2014).

Despite these encouraging findings, there is room for improvement in the ORR, particularly the CR rate, with the majority of patients with metastatic melanoma, NCSLC, and CRC, populations of patients with a poor prognosis, remaining unresponsive to treatment with anti-PD-1/PD-L1 therapies.

Combination approaches with anti-PD-1/PD-L1 therapies and cytotoxic chemotherapy, anti-angiogenic agents, alternative immune-checkpoint inhibitors, immunostimulatory cytokines, and cancer vaccines, are currently under investigation, with the goal of improving efficacy over that seen with monotherapy (Philips 2015).

4.1 Study Treatment

4.1.1 Entinostat (SNDX-275)

SNDX-275, an orally available synthetic pyridylcarbamate licensed from Bayer Schering AG by Syndax Pharmaceuticals and previously named MS-275, inhibits histone deacetylases (HDACs). SNDX-275 promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes. This ultimately leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis (Hess-Stumpp 2007).

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

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

Entinostat inhibited HDAC in various tumor cell lines. In particular, entinostat induced accumulation of acetylated histones adjacent to the promoter of the transforming growth factor (TGF)-β type II receptor

gene, with resulting gene expression. Mutations affecting the TGF-β signaling pathway have been associated with development and progression of human malignancies, including carcinomas of the lung, breast, prostate, and colon. Entinostat also induced histone hyperacetylation and induced expression of various tumor suppressor genes. Various *in vitro* studies in a range of human cancer cell lines have demonstrated the antiproliferative activity of entinostat. *In vivo*, entinostat inhibited the growth of a range of human tumor xenografts, including models of lung, prostate, breast, pancreatic, renal cell, and glioblastoma.

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

4.1.1.1 Entinostat in Patients with Solid Tumors, including Lung Cancer and Melanoma

To date, entinostat has been investigated alone or in combination in >1055 patients with cancer in clinical studies, including >600 patients with solid tumors, including NSCLC and melanoma.

Entinostat has been investigated specifically in patients with NSCLC in combination with erlotinib in clinical studies sponsored by Syndax and in combination with 5-azacitadine (AZA) in clinical studies sponsored by the NCI. Of the studies of entinostat in combination with AZA, evidence of the anti-tumor activity of this combination was demonstrated in an initial study (Juergens 2011), in which adults with metastatic NSCLC who experienced disease progression after at least 1 anticancer regimen received 7 mg of entinostat by mouth (PO) on Days 3 and 10 and 30 or 40 mg/m^2/day of AZA subcutaneously (SC) on Days 1-6 and 8-10 of a 28-day cycle. Of 31 evaluable patients, 1 experienced a CR, with a duration of 14 months; a second patient experienced a PR, with a duration of 8 months; and 10 patients experienced stable disease for at least 12 weeks. Furthermore, 4 patients had major objective responses to the immediate subsequent therapy. Based on these encouraging findings, the NCI has initiated a follow-up study utilizing this combination regimen to investigate the premise that epigenetic therapy can augment the clinical utility of cytotoxic therapy in patients with advanced disease.

Evidence of the efficacy of entinostat also was seen in patients with Stage IV nonresectable melanoma, with 25% of patients experiencing disease stabilization (Hauschild 2008). Based on these encouraging findings, further investigation of entinostat in combination was considered warranted in patients with melanoma.

Overall, among all patients treated, entinostat has been well tolerated at the doses and schedules investigated. Regardless of indication and regimen, the most frequently reported AEs with entinostat included gastrointestinal (GI) disturbances, primarily nausea with or without vomiting and diarrhea; fatigue; and hematologic abnormalities, primarily anemia, thrombocytopenia, neutropenia, and leukopenia. Most occurrences of these events are Grade 1 or 2 in severity and non-serious. Grade 3 and 4 hematologic abnormalities are commonly seen in patients with hematologic malignancies, but are much less prevalent in patients with solid tumors.

As would be expected, the AE profile of entinostat when given in combination varies somewhat based on the agent with which it is given and the corresponding patient population. Entinostat in combination with AZA was generally associated with an increased number and rate of AEs relative to its use in combination with an aromatase inhibitor, erlotinib, or other agents. Consistent with the overall AE profile of entinostat, nausea with or without vomiting, fatigue, and anemia were the most prevalent AEs regardless of the patient population or the agent given in combination.

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

4.1.2 Pembrolizumab (MK-3475)

4.1.2.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

For more details on specific indications refer to the Investigator's Brochure (IB).

4.1.2.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies. In particular, the presence of $CD8^+$ T cells and the ratio of $CD8^+$ effector T cells/forkhead box P3 $(FoxP3)^+$ regulatory T cells seem to correlate with improved prognosis and long-term survival in solid malignancies

such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley 2005; Hunder et al., 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 and CTLA-4, that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald 2005; Okazaki 2001).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta, protein kinase C-theta, and zeta chain-associated protein kinase, which are involved in the CD3 T cell signaling cascade (Okazaki 2001; Chemnitz 2004; Riley 2009; Sheppard 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins (Parry 2005; Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC, melanoma, and colorectal cancer.

4.1.2.3 Preclinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific $CD8^+$ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano 2005; Blank 2004; Weber 2010; Strome 2003; Spranger 2014; Curran 2010; Pilon-Thomas 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome 2003; Curran 2010; Pilon-Thomas 2010; Nomi 2007; Zhang 2009). In such studies, tumor infiltration by $CD8^+$ T cells and increased interferon-gamma (IFN-γ), granzyme B, and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved

local infiltration and activation of effector T cell function *in vivo* (Curran 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the current pembrolizumab IB).

4.2 Study Rationale

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

It was hypothesized that the tumors in animals that did not respond to treatment might have down-regulated the expression of major histocompatibility complex-I-related genes through epigenetic silencing in tumor cells. To evaluate this possibility, animals bearing large CT26 tumors were treated with entinostat+AZA. Eradication of primary tumors was seen in 10 of 11 mice, with a 100% survival rate at 60 days after tumor implantation. Similarly, treatment of mice with moderately-sized 4T1 tumors with anti-PD-1/anti-CTLA-4+entinostat+AZA resulted in complete regression of all primary tumors 3 weeks after treatment initiation and a 80% survival rate at 100 days after tumor implantation. Temporary, self-limiting toxicity, as indicated by body weight changes, was observed in animals exposed to entinostat.

Functional studies revealed that the primary targets of epigenetic modulation were MDSCs, which are often elevated in tumor-bearing hosts and have potent immunosuppressive activities. Specifically, treatment of granulocytic MDSCs (G-MDSCs) with entinostat *in vitro* resulted in markedly reduced viability in a dose-dependent fashion. In contrast, AZA had no effect at comparable concentrations. Importantly, entinostat had only modest effects on $CD8^+$ T cells, creating a large therapeutic window in which G-MDSCs can be depleted while sparing $CD8^+$ T cells.

When co-cultured with $CD8^+$ T cells, G-MDSCs inhibited IFN-γ secretion. However, when entinostat was included in the culture medium, entinostat reverted this inhibition in a dose-dependent manner. These data

support the premise that G-MDSCs directly inhibit the function of CD8+ T cells and that entinostat alleviates this inhibition by directly suppressing G-MDSCs.

In consideration of these nonclinical findings showing that entinostat reduced the number and inhibited the function of host immune suppressor cells, thereby enhancing the anti-tumor activity of immune checkpoint blockade, it is hypothesized that entinostat combined with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab) will result in an improved response rate for the combination compared to either agent alone.

4.3 Rationale for the Dose Selection

4.3.1 Entinostat

Entinostat has been evaluated *in vitro*, in nonclinical *in vivo* studies, and in Phase 1 and 2 studies in patients with various solid tumors and hematological malignancies at doses between 2 and 12 mg/m^2 and at dosing frequencies ranging from once daily to every 2 weeks. Increased histone acetylation was observed at the lowest dose evaluated with the effect persisting at least 48 hours post-dose. Pharmacokinetic (PK) studies of entinostat have indicated a long half-life of entinostat, ranging from 40 hours to 120 hours. Consistent with this long half-life, entinostat concentrations were detectable 168 hours post-dose at doses of 2 to 12 mg/m^2.

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

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

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

Based on the clinical experience with entinostat, a low, fixed dose of 3 mg given weekly has been selected as the starting dose for this study, with escalation to 5 mg weekly planned.

4.3.2 Pembrolizumab

The dose of pembrolizumab planned to be studied in this trial is 200mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma and NSCLC patients is 2mg/kg Q3W. Information on the rationale for selecting 200mg Q3W is summarized below.

KEYNOTE-001was Phase I study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1mg/kg, 3mg/kg and 10mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2mg/kg Q3W and 10mg/kg Q3W in patients with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2mg/kg versus 10mg/kg every 3 weeks (Q3W) have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10mg/kg every 2 weeks (Q2W) has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200mg every 3 weeks (Q3W) is expected to provide similar responses to 2mg/kg Q3W, 10mg/kg Q3W, and 10mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2mg/kg and 10mg/kg. Exposures for 200mg Q3W are expected to lie within this range and will be close to those obtained with 2mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200mg fixed dose are predicted to considerably overlap those obtained with the 2mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in

clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200mg Q3W as the appropriate dose for pembrolizumab.

4.4 Hypothesis

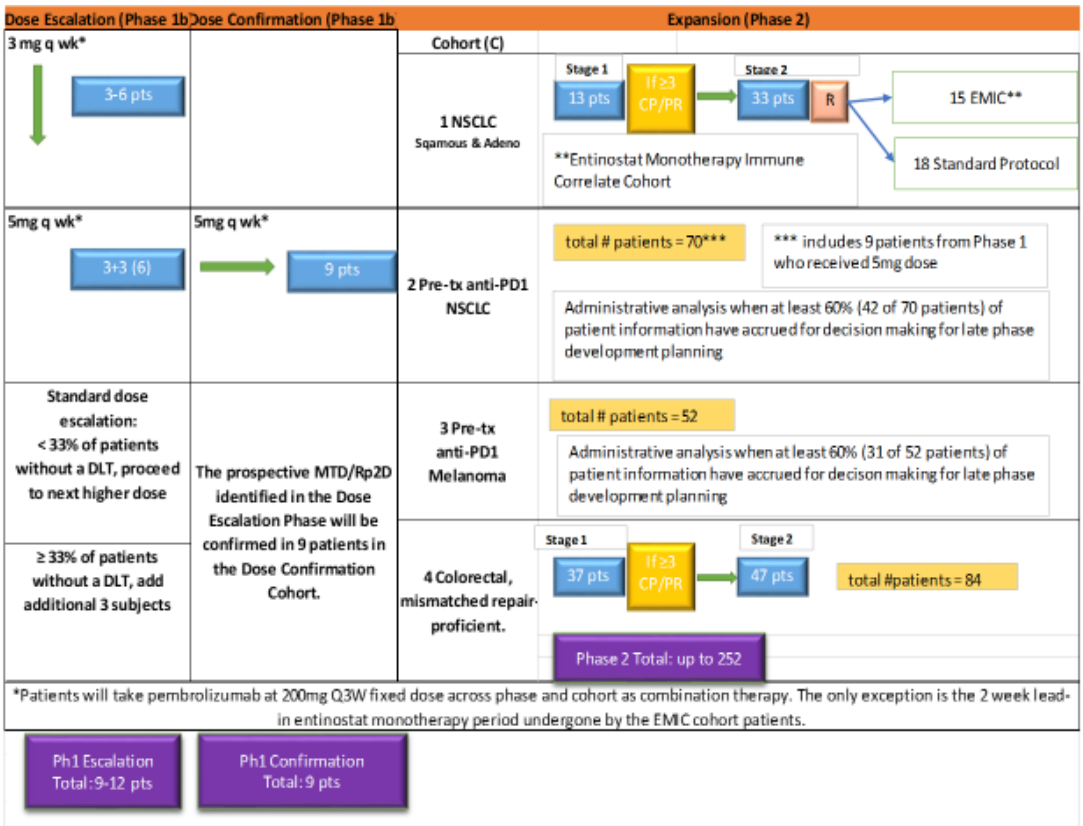
Entinostat has been shown in preclinical models to reduce the number and inhibit the function of host immune suppressor cells in order to enhance the anti-tumor activity of immune checkpoint blockade. It is hypothesized that entinostat combined with pembrolizumab will result in an improved response rate for the combination compared to either agent alone. Preclinical study data suggest that entinostat specifically targets MDSC and thus would improve the response to PD-1/PD-L1-blocking antibody (i.e., pembrolizumab) treatment. The Sponsor accordingly proposes to evaluate populations of MDSC and other myeloid cells in peripheral blood and tumor tissues as well as basic T-cell function in patients, with the expectation that if the MDSC level is decreased, the response to antigens would be improved.

5. EXPERIMENTAL PLAN

5.1 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 cohorts 1 and 4, and utilizing a single proportion binomial test for cohorts 2 and 3An 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 5-1.

Figure 5-1 Study Schema



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 total of 15 patients will be enrolled in an EMIC Cohort. EMIC patients will be enrolled in the study within 3 days of starting of starting entinostat on Day -14 and will participate in a 2-week entinostat monotherapy period. The purpose of this 14-day lead-in phase is to obtain pre-and post-entinostat monotherapy correlative data in blood and tissue. After completion of the 2-week entinostat monotherapy period, patients in the EMIC Cohort will start entinostat in combination with pembrolizumab on C1D1. Patients in the EMIC Cohort will receive entinostat beginning at 5mg weekly for the monotherapy period, and then will receive entinostat in combination with pembrolizumab at the RP2D as identified in the Phase 1b Dose Escalation/Confirmation portion of the study.

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.

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

Blood for immune correlates is to be collected from patients in the EMIC Cohort pre-dose on D-14, C1D1, C1D8, and C2D15. In all other cohorts, blood for immune correlates is to be collected pre-dose on C1D1, C2D1, and C2D15. Blood for protein lysine acetylation and for entinostat and pembrolizumab PK assessments will be collected according to the Schedule of Events. 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 study laboratory manual.

Patients will have radiological disease assessments performed during screening and every 6 weeks (+/-3 days) (Week 6, Week 12, etc.) during treatment. 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.

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

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.

Phase 1b (Dose Escalation/Confirmation): The Dose Escalation/Confirmation Phase of the study, in which patients with NSCLC will be enrolled, employs a classical 3+3 design, with the determination of DLT and the MTD and/or RP2D based on entinostat in combination with pembrolizumab in C1.

Although decisions regarding dose escalation will be made primarily based on review of data from C1, safety data will also be collected from all patients continuing treatment and these data will be reviewed in an ongoing manner by the Sponsor Study Physician(s) in consultation with the Investigators. Any detected cumulative toxicity may require later dose reductions and/or other changes to the dosing schedule, as appropriate, including further refinement of the RP2D.

The initial 3-6 patients will receive entinostat at a starting dose of 3 mg on D1, D8, and D15 along with pembrolizumab 200 mg via intravenous (IV) infusion on D1 of a 21-day cycle. Assuming an acceptable safety profile, escalation to an entinostat dose of 5 mg weekly is planned, keeping the pembrolizumab dose constant. However, based on evaluation of the safety and tolerability data of the previous dose level, it may also be decided that accrual will take place at an intermediate dose level or alternate dosing schedule.

Toxicities will be assessed by the Investigator using the US NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. The decision regarding whether to proceed to the next dose level

will be made by the Sponsor Study Physicians, in consultation with the Investigators after the majority of safety assessments for each cohort are completed. Refer to Section 8.2.1.1 for details regarding the dose escalation procedures.

The prospective MTD/RP2D identified in the Dose Escalation Phase will be confirmed in 9 patients in Dose Confirmation Cohort to obtain additional AE, immune correlate, and anti-tumor activity data on entinostat in combination.

Six patients will need to be treated in a dose level for that dose to be considered for the Dose Confirmation stage. The recommended dose for Phase 2 investigation will be the higher of either 3 or 5 mg weekly PO that results in less than a 33% incidence of DLT. The final determination of the RP2D will be based on a review of all data obtained from both the Dose Escalation and Confirmation Phases and will consider both acute and cumulative toxicities; the incidence of required dose delays, reductions, and discontinuations; and the overall facility of administration in clinical practice.

Patients who experience a DLT will be allowed to remain on study if they meet the following criteria: (1) the Investigator believes it is appropriate for patients to remain on study; (2) the event has resolved and no longer meets the definition of DLT; and (3) the timeline for resolution falls within the guidelines for dose delays (Section 8.4).

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

After completion of the Dose Escalation/Confirmation Phase of the study, with identification of the MTD or RP2D, the Phase 2 portion of the study will commence.

Phase 2 (Expansion): In the Expansion Phase, entinostat in combination will be evaluated using the RP2D identified in the Dose Escalation/Confirmation Phase. Up to 4 Expansion Cohorts consisting of distinct subsets of patients with solid tumor cancers may be explored. Each cohort evaluated during the Expansion Phase will employ a Simon 2-stage design. The final decision about which Expansion Cohorts to study will be based on data from the Dose Escalation/Confirmation Phase, emerging clinical data from other studies, and/or nonclinical data. Expansion cohorts may include:

1. Cohort 1: NSCLC, with squamous cell or adenocarcinoma histology who have not been treated with a PD-1 or PD-L1 blocking antibody[1]

[1] *Depending upon emerging data, the Sponsor may elect, instead of histology, to evaluate NSCLC consisting of PD-1+ and PD-L1+ NSCLC patients. In this case, the protocol will be amended accordingly.*

2. Cohort 2: Patients with NSCLC (any histology) who have previously been treated with and unequivocally progressed on either a PD-1 or PD-L1-blocking antibody
3. Cohort 3: Patients with melanoma who have previously been treated with and unequivocally progressed on either a PD-1 or PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A])
4. Cohort 4: Patients with CRC (mismatch repair-proficient) who have not been previously treated with a PD-1 or PD-L1 blocking antibody

5.2 Number of Centers

Up to approximately 40 study centers are planned to be recruited for participation in this study. Study centers that do not enroll at least 1 patient within 3 months of study center initiation may be subject to closure.

5.3 Number of Patients

In the dose-escalation phase, 3 to 6 patients will be enrolled in each dose cohort based on a standard "3+3" Phase 1 dose escalation scheme. Each patient will participate in only 1 dose 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 other dose recommended for further investigation in Phase 2 (i.e., RP2D) in combination.

Thus, 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.

In the Expansion Phase, up to 252 patients are planned to be enrolled among the 4 Expansion Cohorts (Section 5.1).

5.4 Estimated Study Duration

The estimated duration of the study is approximately 30 months.

6. PATIENT ELIGIBILITY

6.1 Inclusion Criteria

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

Patients with NSCLC:

1. Has histologically- or pathologically-confirmed recurrent or metastatic NSCLC.
2. If has adenocarcinoma, required to have previously been tested for anaplastic lymphoma kinase (ALK) rearrangements and epidermal growth factor receptor (EGFR) (Exon 19 Deletion and Exon 21 L8585R Substitution) mutations, with results available for collection in this study, and, if positive, has been treated with prior EGFR or ALK therapy.
3. Received at least 1 chemotherapeutic regimen in the advanced/metastatic setting and experienced documented, unequivocal progressive disease by either RECIST 1.1 or clinical assessment. In addition:
    - If patient has EGFR mutation-positive or ALK translation-positive disease, must have received an EGFR inhibitor or ALK inhibitor, respectively, in addition to the above chemotherapy regimen.
    - Patients who received adjuvant or neoadjuvant platinum-based doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible; in such cases, the adjuvant or neoadjuvant platinum-based doublet chemotherapy regimen will count as a line of therapy.
    - Patients with recurrent disease >6 months after adjuvant or neoadjuvant platinum-based doublet chemotherapy who subsequently experienced PD during or after a platinum-based doublet chemotherapy regimen given to treat the recurrences, are eligible; the second platinum-based doublet chemotherapy regimen does not count as another line of therapy.
    - Patients who received pemetrexed, bevacizumab, or erlotinib as maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and subsequently progressed after maintenance therapy) are eligible; such therapy does not count as a line of therapy. However, if the patient received a tyrosine kinase inhibitor (TKI) after failure

of platinum-based doublet chemotherapy, the TKI will count as an additional line of therapy.

4. Patients with NSCLC enrolled in Cohort 1 of the Expansion Phase should not have been previously treated with a PD-1/PD-L1-blocking antibody (i.e. pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL320A]

Patients in Expansion Phase, Cohorts 2 (NSCLC) and 3 (Melanoma)

5. Previously treated with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A]) and experienced documented, unequivocal radiographic progression of disease by irRECIST, or similar criteria during or within 12 weeks after last dose of such treatment. Patients must have received at least 6 weeks of PD-1/PD-L1 therapy for Cohort 2 and at least 8 weeks of PD-1/PD-L1 therapy for Cohort 3. For patients who received such agents in a clinical trial, documentation of progressive disease requires a confirmatory scan. For patients who had been treated with such agents outside of a clinical trial, documentation of progressive disease will be based on both radiographic and clinical assessment. If the requirement for a confirmatory scan is deemed not to be in the patient's best interests based upon his/her overall condition, including performance status and clinical symptoms, this requirement may be waived in consultation with the Sponsor's Medical Monitor; however, patients who have not had a confirmatory scan because of rapid progression and clinical deterioration should not be enrolled onto this trial. In all cases, the scan obtained during the screening process may serve as the confirmatory scan.

(Note: Patients who are currently receiving pembrolizumab and have clear, unequivocal evidence of PD may be eligible. Such patients are to be discussed with the Medical Monitor on a case-by-case basis prior to enrollment of the patient in the study.)

Patients with Melanoma

6. In addition to previous treatment with a PD-1/PD-L1 blocking antibody (inclusion #5), has a histologically- or cytologically-confirmed diagnosis of unresectable or metastatic melanoma and experienced unequivocal progressive disease during treatment with a BRAF inhibitor if BRAF V600 mutation-positive. Treatment with BRAF inhibitor may occur AFTER treatment with the checkpoint inhibitor.

Patients in Expansion Phase, Cohort 4 (Colorectal Cancer)

7. Received at least 1 chemotherapeutic regimen in the advanced/metastatic setting and experienced documented, unequivocal progressive disease by either RECIST 1.1 or clinical assessment. Must have documented mismatch-repair proficient colon cancer as determined by either immunohistochemistry for mismatch repair proteins or PCR-based functional microsatellite instability. Patients with colorectal cancer enrolled in Cohort 4 should not have been previously treated with a PD-1/PD-L1-blocking antibody (i.e., pembrolizumab, nivolumab, MEDI4736, or GNE PDL1 [MPDL3280A])

All Patients

8. Aged 18 years or older on the day written informed consent is given.
9. If has brain metastases, must have stable neurologic status following local therapy (surgery or radiation) for at least 4 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent), and must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs. (Patients with a history of carcinomatous meningitis are not eligible.)
10. Evidence of locally recurrent or metastatic disease based on imaging studies (e.g., CT, MRI) within 28 days before the first study drug dose:
    - At least 1 measurable lesion ≥20 mm by conventional techniques or ≥10 mm by spiral CT scan or MRI, with the last imaging performed within 28 days before the first study drug dose. If there is only 1 measurable lesion and it is located in previously irradiated field, it must have demonstrated unequivocal progression according to RECIST, version 1.1.
11. If receiving radiation therapy, has had a 2-week washout period following completion of the treatment prior to receiving the first study drug dose and continues to have at least 1 measureable lesion, per above criterion.
12. ECOG performance status of 0 or 1.

13. Has the following laboratory parameters:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[1] creatinine clearance (CrCl) (glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5× the upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels >1.5× institutional ULN
Hepatic	
Total bilirubin	≤1.5×ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5×ULN
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5×ULN **OR** ≤5×ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

14. Female patients of childbearing potential must have a negative serum pregnancy test during screening and a negative urine pregnancy test within 72 hours prior to taking first dose of study drug. If a patient is of childbearing potential, the patient must agree to use effective contraception as defined in the protocol (Section 8.5.3), during the study and for 120 days after the last dose of study drug. Non-childbearing potential is defined as (by other than medical reasons):

- ≥45 years of age and has not had menses for >2 years,
- Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation.
- Post hysterectomy, oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 adequate barrier

methods throughout the study, starting with the screening visit through 120 days after the last dose of study drug. Please see Section 8.5.3, Contraception, for a list of acceptable birth control methods.

15. If male, agrees to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug. Please see Section 8.5.3, Contraception, for a list of acceptable birth control methods.
16. Experienced resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If patient underwent major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
17. Willing to have fresh tumor samples collected during screening and at other time points designated as mandatory, per the Schedule of Study Assessments. 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.
18. Able to understand and give written informed consent and comply with study procedures.

6.2 Exclusion Criteria

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

1. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
2. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
3. History of interstitial lung disease (ILD).
4. Allergy to benzamide or inactive components of entinostat.
5. History of allergies to any active or inactive ingredients of pembrolizumab or severe hypersensitivity (≥Grade 3) to pembrolizumab.
6. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of

the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator, including, but not limited to:

- Myocardial infarction or arterial thromboembolic events within 6 months prior to baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QTc interval > 470 msec.
- Uncontrolled heart failure or hypertension, uncontrolled diabetes mellitus, or uncontrolled systemic infection.
- Another known additional malignancy that is progressing or requires active treatment (excluding adequately treated basal cell carcinoma, squamous cell of the skin, cervical intraepithelial neoplasia [CIN]/cervical carcinoma *in situ* or melanoma *in situ* or ductal carcinoma *in situ* of the breast). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Active infection requiring systemic therapy.
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 2 weeks prior to the first dose of study drug or are on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent). This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
8. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
9. Received a live virus vaccination within 30 days of the first dose of treatment.

10. Prior anti-cancer mAb within 4 weeks prior to baseline or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

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

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

    Note: If patient underwent major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

12. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks of the first dose of study drug.

13. Currently receiving treatment with any other agent listed on the prohibited medication list in Section 8.5.1 such as valproic acid, or other systemic cancer agents within 14 days of the first dose of treatment.

14. If female, is pregnant, breastfeeding, or expecting to conceive, or if male, expects to father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study drug.

15. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

16. Known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C ribonucleic acid [qualitative]).

17. For CRC expansion cohort, prior history of malignant bowel obstruction requiring hospitalization in the 6 months prior to enrollment

18. For the CRC expansion cohort, history of uncontrolled ascites, defined as symptomatic ascites and/or repeated paracenteses for symptom control in the past 3 months

7. PATIENT ENROLLMENT

Section 14.3 describes documentation required prior to the commencement of study enrollment.

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

After a patient has been screened and successfully fulfills all eligibility criteria, a site representative will send eligibility information to the appropriate Syndax representative. Once the information has been reviewed, approved, and returned to the site, the site representative will enter the patient in the electronic data capture (EDC) system. This will officially enroll the patient. Additionally, this process will automatically assign the patient identification (ID) number that will be used to identify the patient throughout the clinical study. This patient ID must be used on all study documentation related to that patient. Refer to the Study Manual for details on this procedure.

8. TREATMENT PROCEDURES

8.1 Study Drug

Regardless of study phase, all patients will receive entinostat in combination with pembrolizumab, with both drugs given in an open-label fashion.

8.1.1 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).

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.

Patients in the EMIC Cohort will first receive entinostat as monotherapy for 2 weeks (D-14 to -1) at 5mg weekly. After completion of the 2-week entinostat monotherapy period, EMIC patients will enter the combination period and will receive entinostat in combination with pembrolizumab (Section 8.1.2) at the RP2D as determined in the Phase 1b Dose Escalation/Confirmation phase beginning on C1D1. If an EMIC Cohort patient requires a dose reduction during the monotherapy period, that patient will start the combination period at the reduced dose (e.g. 3mg).

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

Entinostat is supplied as pink to light red (1 mg) or yellow (5 mg) coated tablets.

Entinostat is to be stored at controlled room temperature (15ºC to 25ºC) in a secure, locked storage area to which access is limited. Entinostat is to be protected from light. Entinostat is not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC).

Unused tablets or empty bottles will be returned to the clinic for accountability purposes. Details of study drug storage and handling may be found in Section 13.1.3.

8.1.2 Pembrolizumab

The pembrolizumab treatment to be used in this study is outlined in Table 8-1.

Table 8-1 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 or, for the EMIC Cohort, Table 1-2).

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).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

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

8.2 Study Drug Dose and Administration

8.2.1 Dose-escalation Phase

The starting dose of entinostat is 3 mg, with escalation to a dose of 5 mg planned. However, based on evaluation of the safety and tolerability data of the previous dose level, it may also be decided that accrual will take place at an intermediate dose level or alternate dosing schedule.

8.2.1.1 Dose Escalation /Confirmation Procedure

Dose Escalation

Toxicities will be assessed by the Investigator using the NCI CTCAE, Version 4.03. The decision regarding whether to proceed to the next dose level will be made by the Sponsor Study Physician(s) in consultation with the Investigators, after the safety assessments for each cohort are completed.

All patients within a cohort are to complete C1, have safety assessments performed through C2D1, and be assessed for DLT before enrollment of the next cohort may commence. If <33% patients within a cohort have a DLT (i.e., <2 of up to 6), then enrollment of the next cohort may commence with approval from the Sponsor Study Physician(s) in consultation with the Investigators. If ≥33% (≥2 of up to 6) of patients within a cohort experience a DLT, then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. Patients who experience a DLT will be allowed to remain on study if they meet the following criteria: (1) the investigator believes it is appropriate for patients to remain on study; (2) the event has resolved and no longer meets the definition of DLT; and (3) the timeline for resolution falls within the protocol guidelines for dose delays.

If a DLT necessitates enrollment of additional patients into a cohort, the Sponsor Study Physician(s) in consultation with the Investigators, will review all safety data for that cohort after all patients have completed C1.

Although decisions regarding dose escalation will be made primarily based on review of data from C1, safety data will also be collected from all patients continuing treatment and these data will be reviewed periodically by the Sponsor Study Physician(s) in consultation with the Investigators. Any detected cumulative toxicity may require later dose reductions and/or other changes to the dosing schedule, as appropriate, including further refinement of the RP2D.

Patients who discontinue from the study for reasons other than study drug-related toxicity before completing C1 may be replaced.

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.

Dose Confirmation

The prospective MTD/RP2D identified in the Dose Escalation Phase will be confirmed in 9 patients in Dose Confirmation Cohort to obtain additional AE, immune correlate, and anti-tumor activity data on entinostat in combination.

After completion of the Dose Escalation/Confirmation Phase of the study, with identification of the MTD or RP2D, the Phase 2 portion of the study will commence.

8.2.1.2 Dose-limiting Toxicity

DLT is defined as the occurrence of any of the following events within the first cycle of treatment (i.e., C1) of entinostat in combination with pembrolizumab that are considered by the Investigator to be at least possibly related to entinostat. A patient that experiences an adverse event meeting DLT criteria in C1 or who receives the full dose of pembrolizumab and all doses of entinostat during C1 without experiencing a DLT is considered a DLT-evaluable patient.

- Grade 4 hematologic and non-hematologic (non-laboratory) toxicities of any duration
- Grade 3 non-hematologic (non-laboratory) toxicity with the exception of Grade 3 nausea, vomiting, and diarrhea that resolve within 3 days following institution of optimal supportive care
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC $<1.0\times10^9$/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour
  - Grade 4 is defined as ANC $<1.0\times10^9$/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

- Grade 4 thrombocytopenia (i.e., platelet count $<25\times10^9$/L)
- Grade 3 thrombocytopenia with clinically significant bleeding
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any AE requiring >2 entinostat doses to be held, an entinostat dose reduction, or entinostat discontinuation
- Concurrent elevation of transaminases and bilirubin consistent with Hy's Law criteria
  Note: The original Hy's Law parameters for treated patients relative to comparator patients have been broadened over time (Kaplowitz and DeLeve 2003, Zimmerman 1999) to include additional parameters, but still require that these 3 criteria be met:
  i. injury: elevation of >3×ULN ALT or AST activity; and
  ii. function: >2×ULN total bilirubin (another clinical marker for function, such as >1.5×ULN INR may be acceptable if the change is clinically significant in the absence of obstruction) without >2×ULN alkaline phosphatase (ALP); and
  iii. clinical verification to ensure effect is health product-induced and not induced by disease or another cause of injury.
- Grade 5 toxicity

8.2.1.3 Maximum Tolerated Dose

MTD is defined as the highest dose level at which <33% of patients experience DLT in C1.

8.2.1.4 Recommended Phase 2 Dose

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

8.2.2 Expansion Phase

In the Expansion Phase, all patients will receive entinostat PO at the RP2D and schedule on D1, D8, and D15 in combination with pembrolizumab 200 mg via IV infusion over 30 minutes on D1 every 21 days.

8.3 Treatment Duration

The maximum duration of treatment for this study is planned to be 35 treatments (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).

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.

8.4 Dose Adjustments

Although entinostat and pembrolizumab have distinct toxicity profiles, they do share some AEs such as fatigue and nausea. There is the theoretical possibility that 1 agent may potentiate the other and hence drug causality will not always be clear. In the event of uncertainty, dose reductions and/or delays will follow the most conservative approach (i.e., delays and/or dose reductions for both drugs) until resolution of the event. No dose reductions will be performed for pembrolizumab. Guidance for delays and or dose reductions for entinostat are presented in Section 8.4.1. Once the entinostat dose is reduced, it cannot be increased. Expected AEs for each agent are summarized in Section 11.1.

8.4.1 Entinostat

8.4.1.1 Nonhematologic Toxicity at Least Possibly Related to Entinostat

The rules outlined in Table 8-2 are to be followed for the management of non-hematologic toxicities that are definitely or possibly due to entinostat alone, with toxicities graded by the Investigator according to the NCI, CTCAE, Version 4.03.

Table 8-2 Non-hematologic Toxicity: Dose Modification for Entinostat

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

Toxicity	Dose modifications
≤Grade 2	Administer symptomatic remedies / start prophylaxis. Dosing of study drug may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.[1] • If toxicity resolves, resume entinostat at the original dose.

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

8.4.1.2 Hematologic Toxicity at Least Possibly Related to Entinostat

The guidelines in Table 8-3 will be followed for determining the timing of cycles based on hematologic status at the time of planned dosing.

Table 8-3 Hematologic Toxicity: Dose Modification for Entinostat

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

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

8.4.2 Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 8-4. (Refer to Section 8.5.2 and the Study Manual for supportive care guidelines, including use of corticosteroids.)

Table 8-4 Pembrolizumab Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

IR AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken to Pembrolizumab	IR AE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

IR AEs	**Toxicity Grade or Conditions (CTCAEv4.0)**	**Action Taken to Pembrolizumab**	**IR AE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyper-glycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

IR AEs	**Toxicity Grade or Conditions (CTCAEv4.0)**	**Action Taken to Pembrolizumab**	**IR AE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyper-thyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thioamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypo-thyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

IR AEs	**Toxicity Grade or Conditions (CTCAEv4.0)**	**Action Taken to Pembrolizumab**	**IR AE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
All other IR AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1]Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8-5.

Table 8-5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.5 Concomitant Therapy

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

Throughout the study, the Investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, such as potassium and phosphorus supplements and antiemetics, with the exception of those listed in Section 8.5.1. Patients must notify the Investigator of all concomitant medications taken through completion of the study (final visit).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (Section 8.5.1). If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patent on study drug requires the mutual agreement of the Investigator, the Sponsor, and the patient.

8.5.1 Prohibited Medications and Medications to be Avoided During the Study

8.5.1.1. Prohibited Medications

The following medications are prohibited during study participation:

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy other than pembrolizumab

- Investigational agents other than entinostat and pembrolizumab
- Prophylactic use of hematopoietic colony stimulating factors are not allowed during the Phase 1b Dose Escalation/Confirmation Phase, but can be used to treat hematological adverse events and for prophylaxis subsequently, per investigator discretion during the Expansion Phase.
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille de Calmette et Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- The use of systemic corticosteroids to treat disease-related complications or co-morbid medical conditions is strongly discouraged. In consultation with the Sponsor, systemic corticosteroids may be administered, at doses no greater than 10 mg prednisone or for no longer than 7 consecutive days if at higher doses, as clinically indicated, to treat acute conditions, (e.g. exacerbations of COPD, pleural effusions, etc.) other than immune-mediated toxicity related to study drug. The corticosteroid regimens used to treat the immune-related toxicity related to study drug are specified in Section 8.5.2.

  The use of physiologic doses of corticosteroids for prolonged periods may be approved in consultation with the Sponsor. The use of inhaled steroids for the management of asthma or the use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) is permitted. Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients may receive other medications that the Investigator deems to be medically necessary.

The exclusion criteria (Section 6.2) describe other medications that are prohibited in this study.

8.5.1.2. Medications to be avoided during the Study

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

- Gastric acid reducing drugs (e.g., histamine receptor antagonists [H2], antacids; see Appendix 2: Concomitant Medications to be Avoided
- Sensitive substrates of CYP1A2, CYP2C8, CYP3A with a narrow therapeutic window (refer to Appendix 2: Concomitant Medications to be Avoided)
- Drugs that are known to inhibit or induce P-gp (refer to Appendix 2: Concomitant Medications to be Avoided)

8.5.2 Rescue Medications & Supportive Care Guidelines for Pembrolizumab

8.5.2.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of PO or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. It is also important to note that the use of corticosteroids for any reason other than immune-mediated toxicities is strongly discouraged, especially during the phase 1 and first two cycles of phase 2 of this trial. Refer to Section 8.5.1 for specific criteria for the allowance of corticosteroids.

For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the Investigator is instructed to follow the Events of Clinical Interest (ECI; Section 11.4.3) reporting guidance but does not need to follow the treatment guidance (as outlined in the Study Manual). Refer to Section 8.4.2 for dose modification guidelines.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

8.5.3 Diet/Activity/Other Considerations

Diet

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

Contraception

Patients (both men and women) should be informed that taking either of the study drugs may involve unknown risks to the fetus (unborn baby) if a pregnancy were to occur during the study. Specifically, Pembrolizumab may have adverse effects on a fetus *in utero*, and it is not known whether pembrolizumab has transient adverse effects on the composition of sperm. In order to participate in the study, patients with reproductive potential must adhere to contraception methods that result in a failure rate of < 1% per year (described below) from the first screening visit throughout the study period during the treatment period and for at least 120 days after the last dose of study treatment (as defined in Section 11.4.1). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

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

For this trial, male patients will not be considered to have reproductive potential only if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

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

Single method (one of the following is acceptable):

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

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

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

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

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

As discussed above, these contraceptive methods must be used for 120 days after the last dose of study drug. In order to participate in the study, patients must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 11.4.1. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

8.5.4 Study Drug Use in Pregnancy

If a patient inadvertently becomes pregnant while on study drug, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 11.4.1.

8.5.5 Study Drug Use in Nursing Women

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

9. STUDY TESTS AND OBSERVATIONS

After provision of written informed consent, patients will be screened for study eligibility within 21 days before the first study drug dose. Patients who are determined to be eligible, based on screening assessments, will be enrolled in the study within 3 days of C1D1 and start entinostat in combination with pembrolizumab, with the exception of those in the EMIC Cohort.

Patients in the EMIC Cohort will enrolled in the study on Day -14 and will participate in a 2-week entinostat monotherapy period. After completion of the 2-week entinostat monotherapy period, patients in the EMIC Cohort will start entinostat in combination with pembrolizumab on C1D1.

A cycle is 21 days in length. 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.

After discontinuation of all study drug, patients will complete an EOT visit within 7 days after the last study drug dose and Safety F/U visits 30 days and 90 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.

Protocol-required tests, observations, and procedures are summarized in Table 1-2 for the EMIC cohort and in Table 1-1 for all other patients.

9.1 Baseline Assessments

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

9.1.1 Demographics

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

9.1.2 Height

Height is to be documented during screening.

9.1.3 Medical History

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

The medical history is to include cancer history, including date of and stage at diagnosis, method of diagnosis, and all previous treatments, including radiation therapy, and response to such treatment. For patients in Cohorts 2 and 3, who have previously been treated and responded and then progressed on either a PD-1 or PD-L1-blocking antibody, the details regarding the previous PD-1 or PD-L1-blocking antibody, date of progression, and criteria used to determine progression, are to be documented on the eCRF.

For patients with NSCLC, if patient has adenocarcinoma, results of prior testing for ALK rearrangements and EGFR (Exon 19 Deletion and Exon 21 L8585R Substitution) mutations are to be documented. For patients with melanoma, result of prior testing for BRAF V600 mutation is to be documented, if available.

For patients in Cohort 4, results of prior testing for KRAS status, NRAS status, BRAF status are to be documented, if available.

Patients in Cohort 4 must have documented mismatch repair proficient status.

9.1.4 Pregnancy Testing

For females of child-bearing potential, a serum pregnancy test is to be performed during screening and a urine pregnancy test should be performed within 72 hours prior to taking the first study drug dose. Results must be available and confirmed to be negative prior to study drug administration. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

9.2 Safety Assessments

9.2.1 Physical Examination

A complete physical examination will be conducted for all patients during screening; at C1D1 (if the screening physical was performed more than 7 days before); and at the EOT (7 days post-last dose) and Safety F/U (30 and 90 days thereafter) visits. If the screening physical examination was performed within 7 days of C1D1 then a symptom-directed physical examination may be performed at on C1D1.

Symptom-directed physical examinations will be performed for all patients on C1D1 (if the screening physical was performed within 7 days before), C1D8, C1D15; D1 and D15 of C2; and on D1 of each subsequent cycle.

9.2.2 Electrocardiograms

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

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

9.2.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse (beats per minute), respiration rate (breaths per minute), and temperature, are to be measured during screening; at D-14 (EMIC Cohort only); on D1 of each treatment cycle; and at the EOT (7 days post-last dose) and Safety F/U (30 and 90 days thereafter) visits.

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

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

9.2.4 Weight

Weight is to be measured during screening; at D-14 (EMIC Cohort only); on D1 of each treatment cycle; and at the EOT (7 days post-last dose) and Safety F/U (30 and 90 days thereafter) visits.

9.2.5 ECOG Performance Status

ECOG performance status is to be assessed during screening; at D-14 (EMIC Cohort only); on D1 of each treatment cycle; and at the EOT (7 days post-last dose) and Safety F/U (30 and 90 days thereafter) visits.

The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 9-1.

Table 9-1 Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores

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

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

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

9.2.6 Clinical Laboratory Tests

Blood samples for hematology and clinical chemistries are to be collected and run locally during screening; at D-14 (EMIC Cohort only); on D1, D8, and D15 of C1; on D1 and D15 of C2; on D1 of each subsequent treatment cycle; and at the EOT visit (7 days post last dose). If screening hematology and clinical chemistry tests are performed within 7 days of C1D1, they need not be repeated at C1D1.

The following analytes are to be measured:

Hematology

White blood cell count (WBC) with differential	Hemoglobin
Red blood cell count (RBC)	Hematocrit
Platelet count	

Clinical Chemistries

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

Blood samples for thyroid function tests, including thyroid-stimulating hormone (TSH), free thyroxine (FT4), and total or free triiodothyronine (T3 or FT3) are to be collected and run locally during screening, every 6 weeks thereafter during treatment starting at C2, and at the EOT visit (7 days post last dose).

In addition, coagulation studies, including PT or INR and aPTT, are to be measured during screening (locally). However, if a patient is receiving coumarin derivatives concurrently with entinostat, Investigators are advised to monitor PT and INR every cycle or as clinically indicated, whichever is more frequent.

In the CRC cohort, blood tumor marker CEA should be drawn on day 1 of each cycle.

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

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

9.2.7 Adverse Events

AEs, as defined in Section 11.2.1, are to be documented from the time of signing the informed consent through 30 days post-last dose, with the exception of Serious Adverse Events, which must be documented through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier (Section 11.4.3). Events meeting the definition of serious (including Events of Clinical Interest) are to be reported as such as described in Section 11.4 and Section 11.4.3.

9.3 Efficacy Assessments

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

The schedule of tumor burden assessments should be fixed according to the calendar, regardless of treatment interruptions. Tumor burden assessments will be performed until progressive disease as per 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 progressive disease is determined as defined by irRECIST, at the discretion of the investigator.

The same method of assessment and the same technique used for study screening (CT scan or MRI) to characterize each lesion must be used at each subsequent post-screening assessment.

9.3.1 Tumor Measurements and Disease Response Assessment

9.3.1.1 Baseline Tumor Measurement and 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. Images should be kept to the calendar schedule and not be delayed for delays in cycles or study drug administration. Disease response in target and non-target lesions will be assessed locally by the Investigator using irRECIST and RECIST 1.1.

Measurable Disease

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

At least 1 measurable lesion:

- ≥10 mm in longest diameter on an axial image by CT scan or MRI with ≤5 mm reconstruction interval
    - If slice thickness is no greater than 5 mm, longest diameter must be at least 2 times the thickness
- ≤20 mm longest diameter by chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferred, even without contrast
- Lymph nodes ≥ 15 mm in short axis on CT scan (CT slice thickness of ≤5 mm)

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

Non-measurable

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

- Masses < 10 mm
- Lymph nodes 10 – 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 exam which cannot be measured by reproducible imaging techniques
- Blastic bone lesions
- Both benign and equivocal ("cannot exclude") findings should not be included

Target versus non-target

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

9.3.1.2 Scan Procedures

Contrast-enhanced CT scans of chest, abdomen, and, as clinically indicated, pelvis are preferred for evaluation of disease status for this study; however, a contrast-enhanced MRI can also be performed if a patient has or develops allergy to iodinated contrast agents.

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

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

CT Scan Procedures

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

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

MRI Scan Procedures

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

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

9.3.1.3 Disease Response Assessment Criteria

Patients will have radiological disease assessments performed every 6 weeks (±3 days) (Week 6, Week 12, etc.) until unequivocal progressive disease or closure of the study by the Sponsor.

All scans will 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 or complete response should be confirmed by a repeat tumor imaging assessment no less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest, 4 weeks after the first indication of response, or at the next scheduled scan (i.e. 6 weeks later), 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. 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.

Clinical stability is defined as the following:

- Absence of symptoms and signs 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, 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 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 9-2 and illustrated as a flowchart in Figure 9-1.

Table 9-2 Imaging and Treatment After 1st Radiologic Evidence of PD

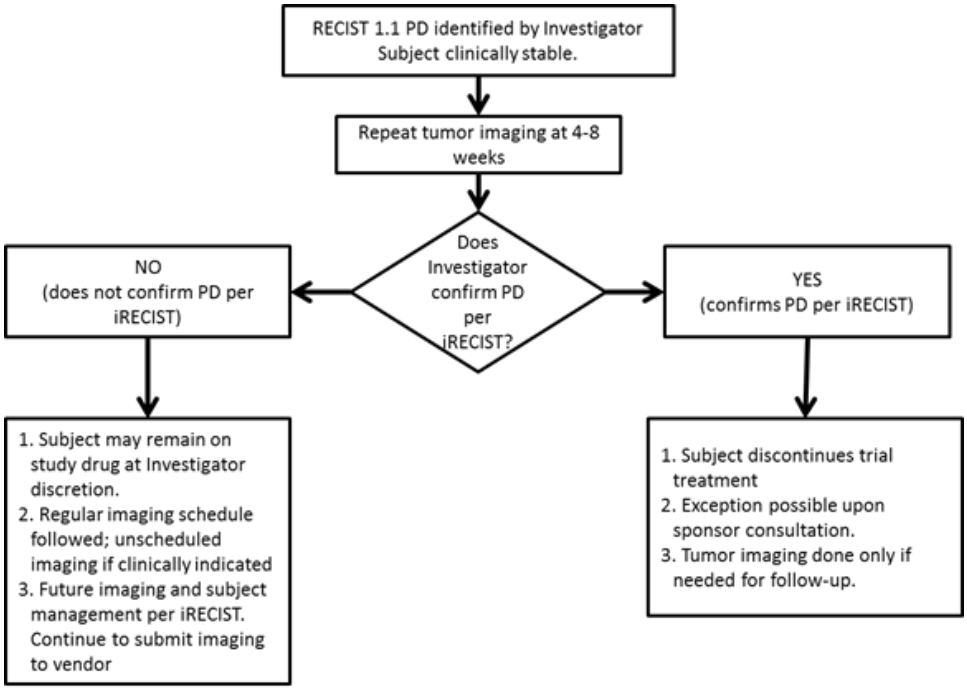
	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	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

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**

Evaluation Criteria in Solid Tumors 1.1.

Figure 9-1: 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.

9.4 Protein Lysine Acetylation and Immune Correlates

Based on preclinical studies it is suggested that entinostat may specifically target a population of MDSCs and thus improve the response to 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.

9.4.1 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-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.

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

9.4.2 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.

Additional details regarding the processing, storage, and shipment of tissue samples for immune correlate assessments are provided in the Study Manual.

9.5 Pharmacokinetics

9.5.1 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.

Instructions for sample collection and shipment will be provided in the PK laboratory manual.

9.5.2 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.

Instructions for sample collection and shipment will be provided in the laboratory manual.

10. DISCONTINUATION AND REPLACEMENT OF PATIENTS

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

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

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

- ineligibility
- withdrawal of consent
- administrative decision by the Investigator or Syndax
- pregnancy
- significant protocol deviation or patient noncompliance
- Unacceptable toxicity
- Confirmed disease progression
- The investigator believes it is no longer in the patient's best interest to continue study therapy

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

Patients who discontinue the study for reasons other than study drug-related toxicity before completing C1 may be replaced.

11. ADVERSE EVENTS, DATA REPORTING, AND RECORDING

11.1 Study Drugs

11.1.1 Entinostat

Commonly encountered AEs across clinical studies of entinostat monotherapy in patients with solid tumors included hypoalbuminemia, fatigue, nausea, hypophosphatemia, anemia, and thrombocytopenia. Incidence and severity were dose- and schedule-dependent. In a Phase 2, randomized, placebo-controlled study in patients with lung cancer, in which patients received erlotinib+entinostat or erlotinib+placebo, treatment-emergent adverse events (TEAEs) occurring at a ≥10% higher incidence in entinostat-treated patients versus placebo-treated patients included nausea (49% versus 25%); anorexia (40% versus 16%); weight decreased (32% versus 18%); dyspnea (31% versus 18%); vomiting (31% versus 13%); peripheral edema (28% versus 13%); anemia (22% versus 11%); thrombocytopenia (15% versus 3%); hypotension (14% versus 2%); and stomatitis (12% versus 2%). In a Phase 2 study in patients with metastatic melanoma treated with entinostat monotherapy, the most common TEAEs were nausea (39%), hypophosphatemia (29%), pain in extremity (21%), and back pain and diarrhea (each 18%) (Hauschild 2008).

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

11.1.2 Pembrolizumab

Please refer to the current Informed Consent, Investigator's Brochure, and the Study Manual for the current safety profile and information regarding pembrolizumab.

11.2 Adverse Event Definitions

11.2.1 Adverse Events

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

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

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

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

In the case of death, only record "Fatal" for the event causing death. AEs that are ongoing at the end of the study or time of death are to be noted as "continuing." Classification of AEs is to be done by the Investigator is according to the NCI CTCAE, Version 4.03. The Death eCRF must also be completed.

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

11.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug Application (IND) safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

11.2.3 Unexpected Adverse Event

An unexpected AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application, as amended.

11.2.4 Serious Adverse Events

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

- is fatal
- is life-threatening (i.e., places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

11.3 Reporting Procedures for All Adverse Events

The Investigator is responsible for ensuring that all AEs (as defined in Section 11.2) observed by the Investigator or reported by patients are properly captured in the patients' medical records and reported on the eCRF. The evaluation time period for all adverse events or events of clinical interest is from the time that the informed consent is signed to at least 30 days after the last dose of entinostat or pembrolizumab, or until resolution of all acute toxicities associated with study drug administration, whichever is longer, with the exception of SAEs, which must be documented through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier (Section 11.4).

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

If applicable, the study drug relationship will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by one of the two drugs based on mechanism of action and/or toxicity profile, or by the combination of entinostat with pembrolizumab?" The causal relation between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

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

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

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

For AEs that are not adequately addressed in the NCI CTCAE, the standard severity grading scale may be used (Table 11-1).

Table 11-1 Standard Severity Grading Scale

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

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

11.4 Serious Adverse Event Reporting Procedures

SAEs will be collected and recorded throughout the study period, beginning with the signing of the informed consent form through 90 days after the last dose of study drug or end of the study (if thought to be related to study drug), or 30 days after the initiation of a new anticancer therapy, whichever is earlier. All SAEs must be reported to Syndax or its representative within 24 hours of discovery or notification of the event. Initial SAE information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and provided to Syndax or its representative. The SAE reporting procedure is provided in the Study Manual.

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

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

11.4.1 Pregnancy and Lactation Reporting Procedures

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study or within 120 days of completing the study or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Study Manual.

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

11.4.2 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

11.4.2.1 Entinostat Overdose

No information on the treatment of overdose of entinostat is currently available. Entinostat overdoses are defined as a single dose greater than 15mg. This overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria as defined in Section 11.2.4. In the event of an entinostat overdose, the Sponsor should be immediately notified. The patient should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

11.4.2.2 Pembrolizumab Overdose

For this study, a pembrolizumab overdose will be defined as ≥5 times the dose for pembrolizumab (e.g., ≥1000 mg). A pembrolizumab overdose is considered an SAE as described in Section 11.4.3. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

11.4.3 Events of Clinical Interest with Pembrolizumab

Selected adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor according to the SAE Reporting Procedures as outlined in Section 11.4. Sponsor Contact information can be found in the Study Manual.

ECIs for this study include:

1. An overdose of pembrolizumab, as defined in Section 11.4.2, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT value that is ≥3×ULN and an elevated total bilirubin value that is ≥2×ULN and, at the same time, an alkaline phosphatase value that is <2×ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria, called the Drug Induced Liver Injury and Overdose Guidelines, can be found in the Study Manual.

11.4.4 Follow-Up of Adverse Events

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

11.4.5 Safety Reporting to Health Authorities, Ethics Committees/Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the EC/IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor or designee will inform the investigator of "findings that could adversely affect the safety of study patients, impact the conduct of the trial, or alter the EC's/IRB's approval/favorable opinion to continue the trial."

When specifically required by regulations and guidelines, the Sponsor or designee will provide appropriate Safety reports directly to the concerned health authority and lead EC / IRB and will maintain records of these notifications. When direct reporting by the Sponsor or designee is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned EC / IRB of any safety reports provided by the Sponsor or designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs / SUSARs / Safety Issues will be carried out in accordance with that Directive and with the related detailed guidance.

11.4.6 Protocol Deviations Due to an Emergency or Adverse Event

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

The Medical Monitor, in conjunction with the Investigators, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted on the eCRF.

11.5 Safety Monitoring

The safety and tolerability of the investigational treatments will be monitored throughout the course of the study by the Investigators and the Sponsor Study Physicians(s) including the Medical Monitor.

The safety and tolerability data that will be reviewed will include, but are not limited to: AEs, DLTs, laboratory test results, and patient discontinuations. Additionally, the development of SAEs will be assessed by the Sponsor Study Physician(s) on a continuous basis. (Note that all SAEs must be reported to the Sponsor or designee within 24 hours of discovery or notification of the event [Section 11.4].)

No formal safety stopping rules are specified in the protocol. However, if any significant safety issues arise, a decision to modify or terminate the study will be made by the Sponsor in collaboration with the Investigators.

12. STATISTICAL CONSIDERATIONS

12.1 Sample Size Estimation

12.1.1 Escalation 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.

12.1.2 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 cohort 1, 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%. For cohorts 2 and 3, the number of responders needed to declare the study a success was based on single proportion binominal test with 90% power and 1-sided significance level of 5%. Note that the protocol may be amended to allow for enrollment of additional or different cohorts, for example, patients with PD-L1-positive NSCLC, based on emerging data during study conduct.

Syndax will conduct one administrative analysis when at least 60% (42 out of 70 patients in cohort 2, 31 out of 52 patients in cohort 3) of patient information have accrued in cohorts 2 and 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 to spend for the first administrative look and leaving 0.04 alpha for the final analysis.

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 for both tumor types. 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 70 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, the single proportion (or one sample) binomial test will be used. Ninety-six percent 1-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 have accrued in cohorts 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 to spend for the first administrative look and 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 52 patients will be enrolled in cohort 3. A true ORR of 25% is hypothesized. An ORR 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, the single proportion (or one sample) binomial test will be used. Ninety-six percent 1-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 have accrued in cohorts 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 to spend for the first administrative look and 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 design elements specified above, up to 37 patients may be enrolled during the first stage: if less 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 out 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%.

12.2 Populations for Analysis

The Full Analysis Set (FAS) will serve as the primary population for the analysis of tumor response and other efficacy-related data. 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

A supportive analysis using the Per-Protocol (PP) set may be performed by excluding patients with important deviations from the protocol that may substantially affect the results of the primary efficacy analyses. The final determination on protocol violations, and thereby the composition of the PP set, will be made prior to locking the clinical database and final analysis and will be documented in a separate memo.

The safety population will be used for the analysis of safety data in this study. The safety population will consist of all patients who receive at least one dose of entinostat and pembrolizumab. At least one laboratory or other safety-related assessment subsequent to at least one dose of entinostat and pembrolizumab is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

A patient that experiences an adverse event meeting DLT criteria during C1 or who receives the full dose of pembrolizumab and all doses of entinostat during C1 without experiencing a DLT, is considered a DLT-evaluable patient.

12.3 Analysis Schedule

12.3.1 Safety Monitoring

The safety and tolerability of the investigational treatments will be monitored throughout the course of the study by the Investigators and Sponsor Study Physician(s) including ongoing review of serious adverse events and other safety trends. Frequent meetings will be held during Phase 1 to review safety aspects of the study and to render dose escalation decisions as applicable.

Safety and tolerability data that will be reviewed by the Sponsor Study Physician(s) will include, but are not limited to: adverse events, laboratory test results, and patient discontinuations. Note that all serious

adverse events must be reported to the Sponsor within 24 hours of discovery or notification of the event. No formal safety stopping rules are specified in the protocol. However, if any significant safety issues arise, a decision to modify or terminate the trial will be made by the Sponsor in collaboration with the study's Steering Committee.

12.3.2 Efficacy Monitoring

An interim analysis of ORR will be performed for each tumor type after enrollment in the first stage is complete in the Expansion Phase. Patients will be followed for response for a minimum of two cycles following the initiation of study drug. Patients who die or discontinue treatment during the first two cycles because of radiographic and/or clinical evidence of disease progression will be considered nonresponders. Enrollment in the second stage will be initiated once enrollment in the first stage is complete and the minimum number of responders is observed, as described in Section 12.1.2. If the minimum is observed prior to the completion of enrollment, then the transition between the first and second stages will occur without interruption. If the minimum is not observed at the time enrollment is completed, then enrollment in the second stage will be held until the continuation criterion is met.

12.4 Statistical Methods

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

The statistical analyses for this study will be performed using SAS® version 9.2 or later (SAS Institute, Inc., Cary, NC). Programming specifications will be prepared which describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of CDISC's Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM). The source SDTM and ADaM datasets from which a statistical analysis is performed (including interim safety and efficacy reviews) will be archived with the Sponsor.

12.4.1 Disposition of Patients

The number of patients included in the efficacy and safety analyses will be summarized, along with the reason for exclusion from one or more analysis populations. Patients discontinuing from study drug and

the primary reason for discontinuation will be summarized. Patients withdrawing from study and the primary reason for withdrawal will be summarized in a similar manner.

12.4.2 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be tabulated by study phase and overall. For the Dose Escalation/Confirmation Phase, tabulations will be provided by dose cohort and overall. For the Expansion Phase, tabulations will be provided by tumor type and overall.

12.4.3 Extent of Exposure

The overall duration of study drug administration (in months) and the total number of cycles initiated will be tabulated for each patient and summarized by study phase. For the escalation phase, tabulations will be provided by dose cohort and overall. For the Expansion Phase, tabulations will be provided by tumor type and overall. For patients who receive entinostat, the average dose of entinostat (in mg) administered and cumulative dose (in mg) administered will be calculated. These data will be further summarized by calculating the mean, standard deviation, median, and range of these values. The number and proportion of patients with one or more dosage modification of study drug will be tabulated by treatment arm along with the reason for dosage modification. The primary reason for study drug discontinuation will be tabulated in a similar manner.

Similar tabulations will be provided for the administration of pembrolizumab.

12.4.4 Concomitant Medications

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

12.4.5 Efficacy Analysis

Efficacy analyses will be conducted using the Full Analysis Set 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 cohorts 1 and 4. 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_L, 1] will be reported since the sample size for the Expansion Phases for cohorts 1 and 4 were determined using a one-sided

significance level of 10%. Crude proportion of patients with best overall response of CR or PR, along with a 2-sided 98% CI, will be calculated for cohorts 2 and 3. CBR at 6 months will be analyzed in a similar manner.

DOR will be calculated for patients who achieve a CR or PR and is defined as the number of months from the start date of the response (and subsequently confirmed) to the first date that recurrent disease or PD is documented. PFS is defined as the number of months from the date of the first dose of study drug to the earliest of documented PD or death due to any cause without prior progression. OS is defined as the number of months from the first dose of study drug to the date of death due to any cause. DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 95% confidence intervals (CIs) calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up. PFS rate at 6 months and corresponding 95% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

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

12.4.6 Immune Correlate Analyses

Immune correlate values will be summarized in a descriptive manner. For immune correlates measured on a continuous scale, the number of patients with non-missing data, mean, either the standard error or standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum values will be presented. For discrete data, the frequency and percent distribution will be presented. Within-patient changes from baseline may be assessed by the Wilcoxon signed rank test and Fisher's exact test, as appropriate. 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 nodes and nodal masses). The association among the various immune correlates and clinical outcomes (data permitting) may be explored using heat map and other data visualization techniques.

12.4.7 Safety Analysis

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, vital signs, and ECG results. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 12.2.

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

TEAEs will be summarized based on the number and percentage of patients experiencing the event by MedDRA (version 18.0) system organ class (SOC) and preferred term. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator based on the conventions described in Section 11.3. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- DLTs (Dose Escalation/Confirmation Phase only)
- all TEAEs
- TEAEs by relationship to study drug and maximum severity grade
- TEAEs with action of study drug delayed/interrupted or dose reduced
- TEAEs with action of study drug discontinued
- SAEs

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

All deaths that occur on study (defined as during treatment or within 90 days of treatment discontinuation) will be reported in a patient listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

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

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

- last post-baseline value

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

Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values. The Wilcoxon signed rank test may be used to assist in the identification of any systematic changes.

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

12.4.8 Pharmacokinetic, Exposure-Safety, and Anti-pembrolizumab Antibody Analyses

A population PK analysis will be used to describe the PK of entinostat. The effects of patient factors (e.g., demographics, clinical chemistries, disease) on entinostat PK will be evaluated. In addition, the relationship between entinostat exposure parameters and indicators of safety will be assessed. Specific details for these analyses as well as analyses of trough pembrolizumab levels and anti-pembrolizumab antibodies will be provided in a separate analysis plan.

12.5 Procedures for Reporting Deviations to the Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

13. INVESTIGATIONAL DRUG PRODUCT

The study drugs being investigated in combination during this clinical trial are pembrolizumab and entinostat. First study treatment is to be administered within 3 days of enrollment into the study.

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

13.1 Entinostat

13.1.1 Description

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

13.1.2 Formulation

Entinostat is supplied in 2 strengths of film-coated tablets containing 1 mg (pink to light red) or 5 mg (yellow) of entinostat as polymorph B. Each tablet contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate as inert fillers. The film coating consists of hypromellose, talc, titanium dioxide, and ferric oxide pigments (red and yellow) as colorants.

Refer to the Pharmacy Manual for more details regarding entinostat.

13.1.3 Storage and Packaging

Entinostat tablets may be shipped and stored at controlled room temperature, up to 25º C (77°F); excursions permitted to 15°C to 30°C (59 – 86°F). The pharmacist will dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers.

13.2 Pembrolizumab

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

Refer to the Pharmacy Manual for details regarding pembrolizumab formulation, storage, packaging and supply.

13.3 Accountability

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

Patient medication instructions and dosing diaries will be provided to the patient for purposes of recording entinostat self-administration. The diaries along with unused entinostat tablets will be returned to the clinic to assess compliance and for entry into the eCRF.

14. REGULATORY OBLIGATIONS

14.1 Informed Consent

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

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

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

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

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

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

14.3 Pre-study Documentation Requirements

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

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

14.4 Patient Confidentiality

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

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

15. ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Protocol Amendments and Study Termination

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

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

15.2 Study Documentation and Archive

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

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

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

- Patient files containing informed consent forms and patient identification list.
- Study files containing the Protocol with all amendments, Investigator's Brochure, copies of pre-study documentation (Section 14.3), and all correspondence to and from the IRB/EC and Syndax.
- Investigational Product Accountability Records and all drug-related correspondence.

In addition, all original source documents supporting entries on the eCRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Syndax and the Investigator. Should the Investigator wish to assign the study records to another party or move them to

another location, he/she must notify Syndax in writing of the new responsible person and/or the new location.

15.3 Study Monitoring and Data Collection

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

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

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

16. REFERENCES

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17. APPENDICES

Appendix 1: New York Heart Association Classification of Heart Failure

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

Appendix 2: Concomitant Medications to be Avoided

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

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

CYP Enzymes	Substrates with narrow therapeutic range[1]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP3A[2]	Alfentanil, astemizole[3], cisapride[4], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[4]

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

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

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

Refer to Table 17-2 for examples of transporter inhibitors and inducers.

Table 17-2 P-gp Inhibitors and Inducers

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

Refer to Table **17-3** for examples of gastric acid reducing drugs.

Table 17-3 Gastric Acid Reducing Drugs[a]

Gastric Acid Reducing Drugs	
H2 Inhibitors	• Cimetidine (Tagamet) • Ranitidine (Zantac) • Famotidine (Pepcid) • Nizatidine (Axid)
Antacids	• Alka-Seltzer • Alka-2, Surpass Gum, Titralac, Tums • Milk of Magnesia • ALternaGEL, Amphojel • Gaviscon, Gelusil, Maalox, Mylanta, Rolaids • Pepto-Bismol

[a] Gastric acid reducing drugs: http://www.everydayhealth.com/ulcer/ulcer-treatment.aspx

Appendix 3: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 9-2 and Figure 9-1). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs 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

Any participant deemed **clinically unstable** should be discontinued from study treatment.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" is in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression

according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

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.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a

decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.