A Phase II Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Entinostat in Combination with Nivolumab plus Ipilimumab in Patients with Renal Cell Carcinoma Previously Treated with Nivolumab plus Ipilimumab or Nivolumab Alone

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 07JUL2021

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	A Phase II Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Entinostat in Combination with Nivolumab plus Ipilimumab in Patients with Renal Cell Carcinoma Previously Treated with Nivolumab plus Ipilimumab or Nivolumab Alone
PHASE	II
OBJECTIVES	**Primary Objective** • Establish the recommended Phase II dose (RP2D) during the Safety Lead-In and to assess efficacy via objective response rate (ORR) via RECIST 1.1 during the Phase II study of entinostat in combination with nivolumab and ipilimumab in patients with advanced renal cell carcinoma who have progressed on nivolumab + ipilimumab regimen or nivolumab alone. **Secondary Objectives** • Characterize safety of entinostat in combination with nivolumab and ipilimumab or nivolumab alone • Estimate ORR via Immune Related Response Criteria (irRC) • Estimate progression free survival (PFS) by RECIST 1.1 and irRC • Estimate overall survival (OS) **Exploratory Objectives** Characterize PD-L1/2, immune cell subsets, and miRs in tumor and/or blood and correlation with response.
STUDY DESIGN	Originally this study was intended as a Phase II, open-label, safety, pharmacodynamics and efficacy study of entinostat in combination with nivolumab and ipilimumab in subjects with advanced renal cell carcinoma (RCC) who have progressed on ipilimumab + nivolumab regimen or nivolumab alone. The clinical study was composed of a two-stage Phase II portion. The Safety Lead-in was to establish the Recommended Phase II Dose (RP2D) in subjects with metastatic RCC. Subjects will be treated with oral entinostat every 7 days continuously, and with nivolumab at a dose of 3 mg/kg mg IV every three weeks in combination with ipilimumab at a dose of 1 mg/kg every 3 weeks × 4 doses. Then, nivolumab 480 mg will be continued every 4 weeks. Subjects that do not tolerate this dosing strategy may receive nivolumab 240 mg IV every 2 weeks. Therefore, each cycle is every 21 days × 4 cycles and then every 28 days thereafter. One dose level of entinostat will be tested in 6-patient cohorts with a dose de-escalation design (5 mg, 3 mg and 2 mg). The 5 mg dose represents 50% of the recommended entinostat

	dose as single agent. The starting dose level of entinostat will be 5 mg PO every 7 days. The first dose level will have a minimum of 6 patients treated. If ≤ 1 dose limiting toxicity (DLT) is observed the study was to move to the Phase II portion and the 6 patients be included in Stage 1 of the Phase II portion. If >1 DLT is observed 6 additional patients will be treated at the lower dose level, etc. DLTs are defined in Section 5.2.1. Due to Funder decision, accrual will halt after enrollment of the safety lead in. This decision is a result of a shift in priorities at the Funder and not due to safety issues. Subjects currently on treatment will continue until criteria as defined in Section 6.2 is met.
KEY ELIGIBILITY CRITERIA **See Section 3 for full eligibility criteria**	• Metastatic renal cell carcinoma with progressive disease on nivolumab + ipilimumab regimen or nivolumab alone. • Adequate hematologic, hepatic, and renal function is required. • ECOG performance status of 0-1. • Life expectancy of at least 6 months.
STATISTICAL CONSIDERATIONS	For the Safety Lead-in, up to 18 subjects could be enrolled. Entinostat will be tested in 3 dose level cohorts (5 mg, 3 mg, or 2 mg). The highest of 3 dose levels of entinostat (either 5mg, 3 mg or 2mg) that results in ≤ 1 out of 6 subject rate of DLT will be the RP2D. For Phase II, assuming a type I error rate of 5% and a power of 90% to compare an uninteresting objective response rate per RECIST 1.1 of 5% while declaring efficacy at 20%, Simon's optimal two stage design enrolls 21 patients in the first stage (with 6 of the 21 from the Safety Lead-in RP2D cohort). If at most one response is seen, then the trial is terminated for futility. Otherwise, accrual continues to a total of 41 patients. If at most 4 patients respond among the 41 patients, the combination would not warrant further investigation. If at least 5 patients respond, this therapy would warrant further investigation. The average sample size is 26.66 and the early termination probability is 71.70% for a drug with a response rate of 5%. All the calculations are based on the R function ph2simon from the package clinfun.
TOTAL NUMBER OF SUBJECTS	N = Due to Funder decision, accrual will halt after enrollment of the safety lead in. This decision is a result of a shift in priorities at the Funder and not due to safety issues. Subjects currently on treatment will continue until criteria as defined in Section 6.7 is met.
ESTIMATED ENROLLMENT PERIOD	12 months

ESTIMATED STUDY DURATION	24 months

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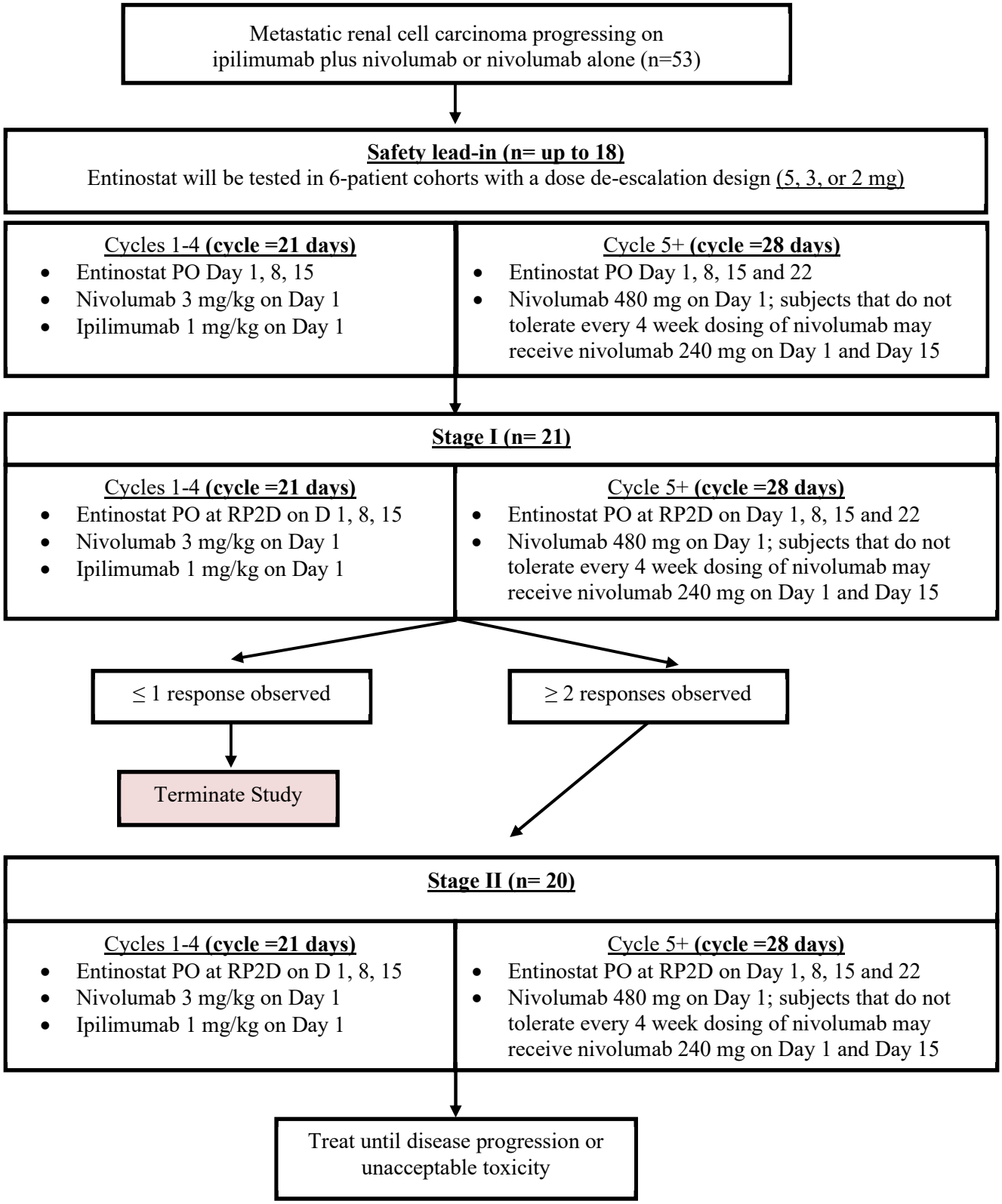
SCHEMA

Due to Funder decision, enrollment will halt after completion of accrual to the safety lead in group. This decision is a result of a shift in priorities at the Funder level and not due to safety issues. Subjects currently on treatment will continue until criteria for discontinuation is met.



1. BACKGROUND AND RATIONALE

1.1 Renal Cell Carcinoma

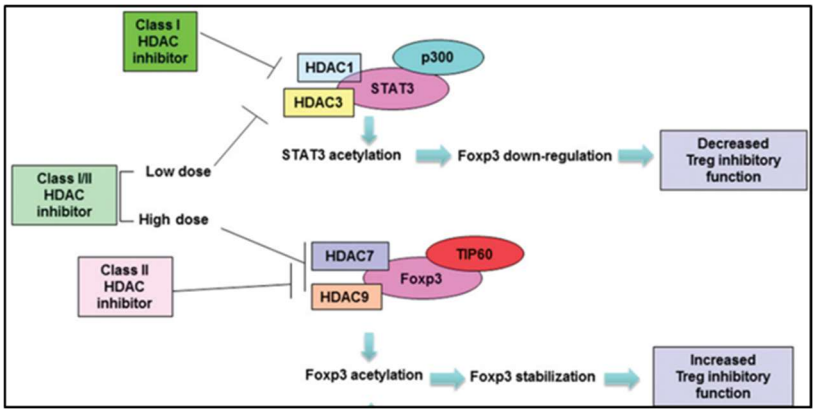
Incidence of renal cell carcinoma (RCC) is reported 338,000 cases worldwide. RCC has a high mortality rate, causing an estimated 144,000 death each year.[1] Approximately 30% of patients are known to have metastatic disease at the time of diagnosis and another one third develop metastatic disease throughout their disease course.[2]

1.2 Background on RCC Treatment

VEGF receptor tyrosine kinase inhibitors represent the standard of care treatment for renal cell carcinoma (RCC). Blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach for the treatment of solid tumors including RCC. PD-1 inhibition has shown single-agent activity in clear cell RCC patients whose disease has progressed following VEGF pathway inhibitor therapy and nivolumab is now approved in RCC previously treated with tyrosine kinase inhibitors.[3] The combination of nivolumab with the CTLA inhibitor ipilimumab also has shown promising activity in RCC.[4] The results from a phase III clinical trial are pending. Though this new class of agents represents a very promising therapeutic strategy only a fraction of patients seems to achieve durable responses.

HDAC inhibitors induce acetylation of several histone and non-histone proteins, which contributes to a wide spectrum of anti-tumor and immunomodulatory activities of this class of agents. Pan HDAC inhibitors have shown either immunosuppressive or immunopromoting properties through modulating cytokine expression, affecting macrophage and dendritic cells, or regulating costimulation molecules. HDAC inhibitors have been also shown to induce activation of major histocompatibility complex (MHC) class I and class II proteins, and co-stimulatory molecules CD40, CD80 and CD86 (Figure 1).

Figure 1: Class I HDAC inhibition decreases Treg function and may enhance immune response. Class I HDAC inhibitors induce acetylation of STAT3 by inhibiting HDAC3 or HDAC1, down regulates Foxp3 gene expression and suppresses Treg function. Class II HDAC inhibitor treatment induces Foxp3 hyper acetylation by targeting HDAC7 and HDAC 9, which leads to stabilization of Foxp3 protein and enhanced Treg function. A pan inhibitor may target Class I HDACs at a low dose and impair Treg function. At a higher dose, the pan inhibitor may target also Class II HDAC and show a dominant Treg promoting effect (Shen L and Pili R Oncoimmunology 2013).

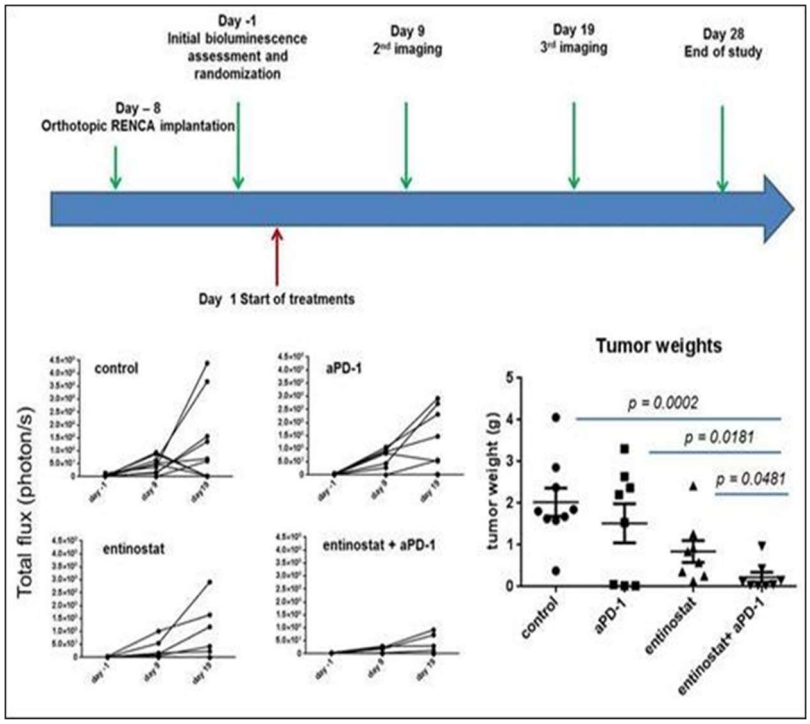


The results from the clinical trials with HDAC inhibitors in cutaneous T-cell lymphoma and large cell lymphoma patients that had led to the approval of vorinostat and romidepsin suggest that the antitumor activity these agents may be in part due to the modulation of the immune response. Our group has reported that the class I HDAC inhibitor entinostat suppresses regulatory T (Treg) cell function, enhances anti-tumor immune response and facilitates cytokine and vaccine immunotherapy in murine renal cell carcinoma and prostate cancer models,

respectively.[5,6] This Treg suppression action does not seem to occur through a depletion mechanism. On further analysis, we observed that entinostat suppresses Foxp3 gene expression in Treg cells and inhibits suppressive function of Treg cells. Entinostat acetylates STAT 3 leading to down regulation of Foxp3. Our preclinical data have shown the synergistic effect of entinostat in combination with high dose interleukin 2 in the RENCA model. Our data also suggest that inhibitors able to modify class I HDACs (class I specific and pan) decrease Foxp3 levels in Tregs in a dose- dependent manner, whereas class II specific HDAC inhibitors did not affect Foxp3 levels. This observation suggests that only class I HDAC inhibition results in Treg suppression.[7,8]

Based on these results, we have completed a CTEP-sponsored phase I/II clinical trial with entinostat in combination with high dose interleukin 2 in patients with RCC (NCT01038778). The phase II results have been recently reported and suggest a biological and clinical activity of this combination.[9] The primary objectives were to evaluate the safety, tolerability and efficacy of this combination strategy. The main eligibility criteria were clear cell histology, no prior treatments, and being fit to receive high dose IL-2. The phase I portion consisted of two dose levels of entinostat (3 and 5 mg, PO every14 days) and a fixed standard dose of IL-2 (600,000 units/kg every 8 hrs). To test our hypothesis, the fixed sample size at the phase II dose level was 36 with a type I/II error of 10%. If 11 or more of the pts have a response, the hypothesis that the response rate is ≤ 20% is rejected. Dose levels 1 and 2 were completed without DLTs and 5 mg was the phase II recommended dose for entinostat. The most common transient grade 3/4 toxicities were hypophosphatemia (16%). lymphopenia (15%), and hypocalcemia (7%) We have enrolled 47 pts (44 at dose level 2), and 37 have completed one cycle (84 days) treatment. Four patients were not evaluable. 13 patients have achieved objective response (35%; 10 PR, 3 CR). To date the median PFS is 16.1 months. Decreased Tregs have been observed following treatment. Preliminary data suggest an association of higher activated antigen presenting cells and monocityc myeloid suppressive cells (MDSCs) with objective responses. The preliminary results from this phase I/II suggest that entinostat may increase the therapeutic effect of high dose IL-2 by modulating immunosuppressive cells.

Figure 2: Entinostat enhances the anti-tumor effect of PD1 inhibition in the RENCA model. Murine renal cell carcinoma cells (RENCA) expressing luciferase were orthotopically implanted. Bioluminescence was assessed at regular intervals (see schema). Tumor bearing animals were randomized to either vehicle, anti-PD1, entinostat or combination. Endpoint tumor weights



Based on these data we have tested the effect of entinostat in combination with PD1 inhibition in a murine model of renal cell carcinoma (RENCA). As shown in figure 2, entinostat enhanced the antitumor effect of anti PD1 antibody treatment. Preliminary data also show that entinostat may inhibit the immunosuppressive activity of MDSC. These data suggest that HDAC inhibition may synergize with immune checkpoint inhibitors.

1.3 Investigational Treatment

1.3.1 Entinostat

Entinostat (SNDX-275, also known as MS-275, ZK244894 and KHK2375) is a novel, potent, orally bioavailable, class I selective histone deacetylase inhibitor (HDACi) that was licensed by Syndax from Bayer Schering Pharma. Entinostat is a substituted pyridylcarbamate with a molecular weight of 376.4 and is classified as an antineoplastic agent.

Entinostat increases the acetylation of histones and other nuclear and cytoplasmic proteins. Although the mechanisms of action are not entirely elucidated, ample evidence has demonstrated that entinostat alters chromatin structure of genes (epigenetic modulation) involved in malignancy to allow for re-expression of tumor suppressor genes, up-regulation of pro-apoptotic genes, down-regulation of cell-survival genes, and down-regulation of oncogenic signaling pathways. These events restore the ability of cells to undergo cell-cycle arrest, differentiation, and apoptosis, restore sensitivity to antineoplastic agents, and reverse malignant characteristics.

1.3.2 Ipilimumab

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Ipilimumab is currently FDA approved in the treatment of unresectable or metastatic melanoma. Ipilimumab is also under investigation for the treatment of subjects with other types of cancer. Studies are being sponsored by Bristol-Myers Squibb, with the US National Cancer Institute (NCI) and Mayo Clinic as additional sponsors.

1.3.3 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.* Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

*Clinical Study Report: Study No. CA209017. An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Company; 2015. Document Control No. 930086504.

1.4 Rationale

Novel strategies to enhance the antitumor activity of immune-checkpoint inhibitors are under development. This study will assess the immunomodulatory activity of entinostat in patients who have progressed while receiving the immune-checkpoint inhibitors nivolumab and ipilimumab or nivolumab alone. The overall hypothesis is that entinostat will restore the immune response and antitumor effect induced by the PD1/CTLA inhibition by suppressing Treg and MDSC function. The schedule of entinostat is based on our previous experience with this agent. Based on our working hypothesis that low dose HDAC inhibitors will have a suppressive function on Tregs and MDSC but not on T effector cells, the starting dose of entinostat will be 5 mg weekly.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

Establish the recommended Phase II dose (RP2D) during the Safety Lead-In and to assess efficacy via objective response rate (ORR) via RECIST 1.1 during the Phase II study of entinostat in combination with nivolumab and ipilimumab in subjects with metastatic RCC who have progressed on nivolumab + ipilimumab regimen.

2.1.2 Secondary Objectives

- Characterize safety of entinostat in combination with nivolumab and ipilimumab
- Estimate ORR via Immune Related Response Criteria (irRC)
- Estimate progression free survival (PFS) via RECIST 1.1 and irRC
- Estimate overall survival (OS)

2.1.3 Correlative Objectives

Characterize PD-L1/2, immune cell subsets, and miRNAs in tumor and/or blood and correlate with response.

2.2 Endpoints

2.2.1 Primary Endpoint

- ORR (rate of complete response (CR) + partial response (PR)) per RECIST v1.1

2.2.2 Secondary Endpoints

- Toxicity will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4
- ORR (rate of irCR + irPR) per irRC

- PFS per RECIST 1.1 is defined from day 1 of treatment until disease progression or death as a result of any cause, with progression defined per RECIST 1.1
- PFS per irRC is defined from Day 1 of treatment until disease progression or death as a result of any cause, with progression defined per irRC
- OS is defined from Day 1 of treatment until death as a result of any cause

2.2.3 Correlative Endpoints

- PD-L1/2
- Immune cell subsets
- miRNAs

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-1 within 28 days prior to registration.

4. Histological or cytological evidence of renal cell carcinoma (initial diagnosis).

5. Metastatic disease.

6. Progressive disease on nivolumab + ipilimumab regimen or nivolumab alone. **NOTE**: Patients who have completed at least one dose of ipilimumab + nivolumab and progress or have completed the 4 doses of ipilimumab + nivolumab and progress during nivolumab monotherapy maintenance are eligible. Patients who have completed at least one dose of nivolumab monotherapy and have progressed are also eligible. Patients who discontinue prior ipilimumab + nivolumab or nivolumab monotherapy for toxicity are excluded.

7. Target lesions according to RECIST v1.1 or non-target bone lesions assessed by bone scan or PET scan.

8. A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off corticosteroids for ≥ 4 weeks, and are asymptomatic.

9. Prior cancer treatment (excluding nivolumab + ipilimumab or nivolumab alone) must be completed at least 28 days prior to start treatment and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia or neuropathy)

to ≤ Grade 1 or baseline. If subject underwent major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

10. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Platelets	≥100 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1.5 x 10^9/L
Hemoglobin (Hgb)	≥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 CrCl) [1] Creatinine clearance should be calculated per institutional standard	≤1.5 x the upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 x institutional ULN
Hepatic	
Bilirubin	≤1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
Aspartate aminotransferase (AST)	≤3 x ULN
Alanine aminotransferase (ALT)	≤3 x ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT/INR/PTT is within therapeutic range of intended use of anticoagulants

11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and a negative urine pregnancy test within 3 days prior to first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a urine test is not required.

12. Women of childbearing potential must be willing to abstain from heterosexual intercourse or to use an effective method of contraception from the time of informed consent until 5 months after the last dose of study drug.

13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drugs and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 3 months after the last dose of entinostat.

14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

15. Life expectancy of at least 6 months per investigator discretion.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator, including, but not limited to:
    - Myocardial infarction or arterial thromboembolic events within 6 months prior to screening or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QTc interval > 470 msec.
    - Uncontrolled hypertension or diabetes mellitus.
    - Another known malignancy that is progressing or requires active treatment.
    - Any prior history of other cancer within the prior 5 years with the exception of adequately treated basal cell carcinoma or cervical intraepithelial neoplasia [CIN]/cervical carcinoma in situ or melanoma in situ).
    - Active infection requiring systemic therapy.
    - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

2. Pregnant or breastfeeding. **NOTE:** breast milk cannot be stored for future use while the mother is being treated on study.

3. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.

4. Allergy to benzamide or inactive components of entinostat.

5. Hypersensitivity to nivolumab, ipilimumab, or any of their excipients.

6. Treatment with any investigational drug or device within 4 weeks prior to registration.

7. Treatment with systemic steroids within 4 weeks prior to registration. **NOTE:** adrenal replacement doses of steroids (equivalent of prednisone 10mg daily) are permitted.

8. Evidence of active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.

9. Interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids.

10. Diagnosis of immunodeficiency; or is receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 4 weeks prior to registration.

11. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies). Testing during screening is not required.

12. Known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative]). Subjects with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA test must be performed in these subjects prior to study treatment, and results must be negative to be eligible. Subjects with a history of hepatitis C must be tested for presence of hepatitis C virus (HCV) antibody. If HCV antibody positive, subjects will only be eligible if polymerase chain reaction is negative for HCV RNA.

13. Has received a live vaccine within 30 days prior to planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy.

5. TREATMENT PLAN

This is a Phase II, open-label, safety, pharmacodynamic and efficacy study of entinostat in combination with nivolumab and ipilimumab in subjects with metastatic RCC who have progressed on ipilimumab + nivolumab regimen or nivolumab alone. Prior to Phase II, a safety lead-in will be conducted to establish the RP2D of entinostat when used in combination with ipilimumab + nivolumab (see Section 5.1). Subjects will initially be treated with the combination of oral entinostat and intravenous (IV) nivolumab plus ipilimumab. Entinostat will be dosed weekly, and nivolumab and ipilimumab will be dosed every 3 weeks, for a total of four, 3-week cycles. Following these first four cycles, entinostat will continue to be administered weekly in combination with nivolumab every 4 weeks or every 2 weeks based on subject tolerance. Ipilimumab will be discontinued. Treatment continued until disease progression or prohibitive toxicity. Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline and every 6-8 weeks thereafter using RECIST version 1.1.

Due to Funder decision, enrollment will halt after completion of accrual to the safety lead in group. This decision is a result of a shift in priorities at the Funder level and not due to safety issues. Subjects currently on treatment will continue until the criteria for treatment continuation as defined above is met.

5.1 Study Treatment Administration

5.1.1 Cycles 1-4 (cycle =21 days)

Drug	Dose	Route	Schedule[1]	Cycle Length
Entinostat	5mg, 3mg, or 2mg [2]	PO	Days 1, 8, 15	21 days
Nivolumab	3 mg/kg	IV over 30 minutes	Day 1	
Ipilimumab	1 mg/kg [3]	IV over 30 minutes	Day 1	

[1] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart or on drug diary and in the electronic case report forms (eCRFs).
[2]See Section 5.2 on the Safety Lead-In for determining the RP2D of entinostat
[3]Use the subject's actual (not ideal) body weight for dosing as per the American Society of Clinical Oncology (ASCO) guidelines on dosing of obese adult subjects. If a subject's weight changes by more than 10% from Cycle 1 Day 1 the dose of nivolumab and ipilimumab should be recalculated.

5.1.2 Cycles 5+ (cycle = 28 days)

Drug	Route	Dose	Schedule[1]	Cycle Length
Entinostat	PO	RP2D [2]	Days 1, 8, 15 and 22	28 days
Nivolumab [3]	IV over 30 minutes	480 mg	Day 1	
		Subjects that do not tolerate every 4 week dosing		
		240 mg	Day 1 and 15	

[1] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart or on drug diary and in the eCRFs.
[2] See Section 5.2 on the Safety Lead-In for determining the RP2D of entinostat
[3] See Section 5.4.2 for additional details regarding nivolumab administration during the maintenance period. Subjects will receive 480 mg on Day 1 of each cycle. Subjects that do not tolerate an every 4 week dosing regimen may receive nivolumab 240 mg on Day 1 and Day 15 of each cycle.

5.2 Safety Lead-In

Entinostat in combination with fixed dose nivolumab and ipilimumab will be tested using a 3+3 dose de-escalation design (5 mg, 3 mg and 2 mg). The starting dose level of entinostat will be 5 mg PO every 7 days, which is 50% of the recommended entinostat dose when used as single agent. Dose limiting toxicities (DLTs) will be evaluated during the first two cycles (6 weeks) of treatment. Each dose level will have up to 6 patients treated.

The trial will proceed in a 3+3 fashion. The study will recruit the first 3 patients starting at the highest dose level (5 mg). If there is 0 or 1 DLT, then the study will recruit additional 3 patients treated at that dose level. If ≤ 1 DLT is observed after 6 patients at this dose, that will be the

RP2D. If any time at this dose level, more than 1 DLT is observed, then the accrual to this dose level will be stopped, and the study will be de-escalated to the next dose level (3mg).

This procedure is repeated at the second dose level cohort (3 mg). At this dose level, the study will study 3 patients first. If there is 0 or 1 DLT, then the study will recruit additional 3 patients treated at that dose level. If ≤ 1 DLT is observed after 6 patients at this dose, that will be the RP2D. If any time at this dose level, more than 1 DLT is observed, then the accrual to this dose level will be stopped, and the study will be de-escalated to the next dose level (2 mg).

Up to 6 patients will be enrolled and treated at the last dose level cohort (2 mg). At this dose level, the study will study 3 patients first. If there is 0 or 1 DLT, then the study will recruit additional 3 patients treated at that dose level. If ≤ 1 DLT is observed after 6 patients at this dose, that will be the RP2D. If any time at this dose level, more than 1 DLT is observed, then the accrual to this dose level will be stopped, and the study will be terminated and no RP2D can be reached.

For the Safety Lead-in, up to 18 patients could be enrolled. The RP2D will be the highest of these 3 dose levels of entinostat that results in ≤ 1 out of 6 subjects experience a DLT. The 6 subjects in the RP2D cohort will be included in Stage 1 of the Simon's optimal two-stage Phase II study.

5.2.1 Dose Limiting Toxicity (DLT)

DLTs are defined as:

- Prolonged (>1 week) Grade ≥ 3 anemia attributable to entinostat and/or nivolumab plus ipilimumab during the first 2 cycles (6 weeks) of the combination treatment.
- Grade 3-4 febrile neutropenia
- Grade 4 thrombocytopenia
  Grade 3 thrombocytopenia with hemorrhage
- Grade 3-4 nonhematological toxicities attributable to entinostat and/or nivolumab plus ipilimumab during the first 2 cycles (6 weeks) of the combination treatment. Exceptions include:
  - Grade 3 fatigue < 7 days
  - Grade 3 nausea lasting < 72 hrs in patients who have not received adequate anti-emetic therapy
  - Grade 3-4 vomiting lasting < 72 hrs in patients who have not received adequate anti-emetic therapy
  - Grade 3-4 diarrhea lasting < 72 hrs in patients who have not received adequate anti-diarrheal therapy
  - Asymptomatic laboratory abnormalities lasting < 72 hrs
  - Asymptomatic elevations in AST or ALT lasting < 7 days.
- AST or ALT > 3 x ULN in patients in whom these abnormalities cannot be attributed to another, non-drug related cause
- Total bilirubin > 2 x ULN in patients whom this abnormality cannot be attributed to another, non-drug related cause

5.3 Phase II

Due to Funder decision, enrollment will halt after completion of accrual to the safety lead in group and not proceed to Phase II. This decision is a result of a shift in priorities at the Funder level and not due to safety issues. Subjects currently on treatment will continue until the criteria for treatment continuation as defined above is met.

The six subjects treated at the RP2D of entinostat from the Safety Lead-in would have been rolled over into Stage 1 of the Phase II portion of the study, and an additional 15 subjects would have been enrolled. If at most one response is seen within Stage 1, then the trial would have been terminated for futility. Otherwise, accrual would have continued to a total of 41 subjects treated at the RP2D. Pre-medication Subjects do not require routine pre-medication prior to each treatment. However, local institutional standards may be followed, at the discretion of the investigator.

See Section 5.6.1 for recommended premedication in subjects who experience infusion related reaction (IRR), allergic reaction or bronchospasm associated with nivolumab and/or ipilimumab.

5.4 Study Drug(s) Administration

5.4.1 Entinostat

Entinostat (5mg, 3mg, or 2 mg) will be administered orally every 7 days. Treatment will continue until disease progression in the absence of prohibitive toxicities.

Entinostat is to be taken on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal. Entinostat tablets should not be split, crushed, or chewed. If entinostat is vomited, dosing should not be re-administered but instead the dose should be skipped. Subjects should record the emesis and the skipped dose in their drug diary. If an entinostat dose is missed, it may be taken up to 48 hours after the scheduled dosing time. If it is not taken within the 48 hour window, the dose should not be taken and should be counted as a missed dose. The subject should take the next scheduled dose per protocol and record the missed dose in their drug diary.

5.4.1.1 Entinostat Compliance

Subjects will complete a diary to document their drug compliance. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at each clinic visit. Site staff will perform accountability of the returned drug, assess subject compliance, and educate the subject on the directions for self-medication.

5.4.2 Nivolumab

Nivolumab 3mg/kg will be administered as a 30 minute IV infusion on Day 1 of each 21 day cycle for 4 cycles. During maintenance, nivolumab will be administered at 480 mg IV on Day 1 of each 28 day cycle. Subjects that do not tolerate an every 4 week dosing regimen may receive nivolumab 240 mg IV on Day 1 and Day 15 of each 28 day cycle. The decision to change the dosing regimen is at the site investigator’s discretion. If a subject transitions to an every 2 week dosing regimen that subject will remain on that dosing regimen for the remainder of their treatment. See Section 5.6.1 for management of any infusion reaction that occurs with nivolumab. Sites should make every effort to target infusion timing as close to 30 minutes as

possible. However, given the variability of infusion pumps from site to site, a window of + 10/-5 minutes is acceptable. Treatment will continue in the absence of prohibitive toxicities or disease progression.

5.4.3 Ipilimumab

Ipilimumab 1mg/kg will be administered as a 30 minute IV infusion on Day 1 of each 21 day cycle for 4 cycles. See Section 5.6.1 for management of any infusion reaction that occurs with ipilimumab.

Sites should make every effort to target infusion timing as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of ± 10/-5 minutes is acceptable. Treatment will continue for up to 4 cycles, in the absence of prohibitive toxicities or disease progression.

Nivolumab will be given first, followed by 30 minutes of monitoring, and then ipilimumab given second, followed by 30 minutes of monitoring. If the subject does not have an infusion reaction during the first cycle, the post-ipilimumab monitoring may be discontinued for subsequent cycles at the discretion of the treating physician. However, monitoring between the nivolumab/ ipilimumab infusions will continue throughout all 4 cycles.

5.5 Concomitant Medications

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Subjects who are still being followed for a serious adverse events (SAE) will have SAE-specific concomitant medications recorded until resolution of the SAE.

5.5.1 Allowed Concomitant Medications

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF. Use of bisphosphonates during study treatment is at site investigator's discretion.

5.5.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The site investigator should discuss any questions regarding this with the sponsor-investigator via the HCRN project manager. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.
The following medications are excluded while the subject is receiving study drugs:

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors

- Any additional anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy, will not be allowed, even if utilized as treatment of non-cancer indications.
- Any therapeutic investigational agents
- 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 Investigator. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, 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.
- Systemic glucocorticoids (>10 mg prednisone equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Inhaled or topical steroids, and adrenal replacement doses of steroids (for example prednisone 10mg daily) are permitted while on study.

5.5.3 Recommendations for Medications to be Avoided

- Sensitive substrates of CYP1A2, CYP2C8, CYP3A with a narrow therapeutic window (see Appendix 1)
- Drugs that are known to inhibit or induce P-gp (see Appendix 1)

5.6 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator.

Suggested supportive care measures for the management of adverse events (AEs) with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous 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. 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 nivolumab or ipilimumab.

5.6.1 Suggested supportive care measures for the management of AEs that are related to nivolumab or ipilimumab

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in Appendix 2. The guidance provided in these algorithms should not replace the site Investigator's medical judgment but should complement it.

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Subjects who are started on steroids for management of an immune-related event should not resume immunotherapy until steroids have been tapered to ≤ prednisone 10mg daily or an equivalent dose of an alternative corticosteroid.

Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab or ipilimumab.

Management of Infusion Related Reaction (IRR), Allergic Reaction, Hypersensitivity reaction or Bronchospasm from Nivolumab or Ipilimumab

Description	Action
CTCAE Grade 1 IRR, allergic reaction or bronchospasm	Remain at bedside and monitor subject until recovery from symptoms. For subsequent infusions, it is recommended that diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes prior to subsequent infusions of nivolumab or ipilimumab. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
CTCAE Grade 2 IRR, allergic reaction or bronchospasm	Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further

	nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. For subsequent infusions, it is recommended that diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes prior to subsequent infusions of nivolumab or ipilimumab. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
CTCAE Grade 3 or 4 IRR, allergic reaction, bronchospasm or hypersensitivity reaction[1]	Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. ***Nivolumab or ipilimumab will be permanently discontinued***. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
[1]Hypersensitivity reactions included in CTCAEv4 include anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis; in the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).	

5.7 Contraception

Women of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL. Women of childbearing potential must be willing to abstain from heterosexual intercourse or to use an effective method of contraception from the time of informed consent until 5 months after the last dose of study drug. This timeframe is applicable to breast-feeding as well.

Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year (i.e., a highly effective contraceptive method). Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 3 months after the last dose of entinostat. This timeframe is applicable to sperm donation.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirements for the duration of the study and during

the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.1 Highly Effective Methods of Contraception

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence: Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

5.7.2 Less Effective Methods of Contraception

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom* without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

* A male and female condom must not be used together

5.8 Use in Pregnancy

If a subject becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to HCRN **within 24 hours** of discovery of event and HCRN will notify the sponsor-investigator**,** Bristol-Myers Squibb (BMS) and Syndax **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 site 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 HCRN who will report to BMS and Syndax. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to HCRN who will report the event to BMS and Syndax and follow as described above.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be used to grade AEs.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

All dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined below based on clinical judgment that is in the best interest of the subject. **NOTE**: if one or more study drugs are permanently discontinued, subjects may continue with the remaining drugs per protocol at the discretion of the treating physician if the subject is receiving clinical benefit.

For subjects with immune-related adverse events (irAEs), if the management guidelines suggest delay or discontinuation, both nivolumab and ipilimumab should be held or discontinued. In the event that ipilimumab must be permanently discontinued due to an AE which can be directly attributed to ipilimumab (e.g. an infusion reaction), nivolumab may be continued per protocol at the discretion of the treating physician.

6.1.1 Entinostat

The dose levels used for dose modifications of entinostat will be 5, 3 or 2 mg PO QW, with the chosen dose based on the starting dose. If a dose below 2mg PO QW is required for entinostat, entinostat must be permanently discontinued, and the subject followed-up per protocol. If a dose of entinostat is held for toxicity and cannot be resumed within 48 hours, the dose will not be made up, and the subject will continue to follow the standard dosing schedule. If the dose of entinostat is held for toxicity and can be resumed within 48 hours, the dose will be given, and the subject will continue to follow the standard dosing schedule (i.e., the next dose will be given on time).

Management of toxicities that are at least possibly related to entinostat will be managed as follows:

Non-hematologic Toxicity	
Toxicity	**Entinostat Dose Modifications**
Grade 4	Administer symptomatic remedies/start prophylaxis. Permanently discontinue 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: a. If receiving 5 mg, restart study drug at 3 mg b. If receiving 3 mg, restart study drug at 2 mg c. If receiving 2 mg, permanently discontinue study drug If not recovered within 4 weeks, permanently discontinue study drug.
Recurrence of the same ≥ Grade 3 toxicity despite dose reduction	If the same ≥Grade 3 event recurs: 1. Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline. 2. If recovered within 2 weeks, resume study drug as follows: a. If receiving 5 mg, restart study drug at 3 mg b. If receiving 3 mg, restart study drug at 2 mg c. 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.
≤ Grade 2	Administer symptomatic remedies / start prophylaxis. Dosing of study drug may be interrupted (held) [1] at the Investigator's discretion. 1. If dose is held for 4 consecutive weeks, permanently discontinue study drug. 2. 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.	

Hematologic Toxicity	
Toxicity	**Entinostat Dose Modifications**
≥Grade 3 neutropenia, ≥Grade 3 febrile 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 direction: 1. If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose. 2. If receiving 2 mg dose, and not recovered by either of the next 2 scheduled doses, permanently discontinue study treatment. Otherwise, skip each dose. If recovered for either of these doses, resume study drug as follows: a. If receiving 5 mg, restart study drug at 3 mg. b. If receiving 3 mg, restart study drug at 2 mg. 3. If not recovered within 4 weeks, 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: a. If receiving 5 mg, restart study drug at 3 mg b. If receiving 3 mg, restart study drug at 2 mg c. 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.	

6.1.2 Ipilimumab

There are no dose reductions for ipilimumab. For toxicity as outlined in this protocol, study therapy should be delayed until the AE improves to the stated level or should be discontinued permanently depending on severity (see table below). If a dose of ipilimumab is held for toxicity and cannot be resumed within 48 hours, the dose will not be made up, and the subject will continue to follow the standard dosing schedule. If the dose of ipilimumab is held for toxicity and can be resumed within 48 hours, the dose will be given, and the subject will continue to follow the standard dosing schedule (i.e., the next dose will be given on time).

6.1.3 Nivolumab

There are no dose reductions for nivolumab. For toxicity as outlined in this protocol, study therapy should be delayed until the AE improves to the stated level or should be discontinued permanently depending on severity (see table below). If a dose of nivolumab is held for toxicity and cannot be resumed within 48 hours, the dose will not be made up, and the subject will continue to follow the standard dosing schedule. If the dose of nivolumab is held for toxicity and can be resumed within 48 hours, the dose will be given, and the subject will continue to follow the standard dosing schedule (i.e., the next dose will be given on time).

Dose delay guidelines for nivolumab related adverse events
Recommendations for nivolumab modifications are below. When nivolumab is administered with ipilimumab, if nivolumab is held then ipilimumab should also be held.

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/ HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue

Adverse Reaction	Severity*	Dose Modification
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

[a] Resume treatment when adverse reaction improves to Grade 0 or 1.

[b] HCC: hepatocellular carcinoma.

[c] Resume treatment when AST/ALT returns to baseline.

Dose delay guidelines for ipilimumab related adverse events

Recommendations for nivolumab modifications are below. When nivolumab is administered with ipilimumab, if nivolumab is held then ipilimumab should also be held.

Mild to moderate adverse reactions	Action
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs, resume therapy.[d] 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment.[d] 4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels	
Skin: Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology	
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	
Neurological: Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions[c]	

[a] No dose reduction of YERVOY is recommended.

[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).

[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. Decision whether to withhold a dose should be based on severity.

[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

ULN = upper limit of normal

6.2 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the eCRF.

- Documented disease progression per RECIST 1.1.
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant

6.3 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

	Screen	Cycle= 21 days				Cycle= 28 days		Safety follow up[13]	Long-term Follow up[14]
	-28 days[1]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5+		30/100 days (±7)	Q 6 months (±30)
		D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D15 ±3[12]		
REQUIRED ASSESSMENTS									
Informed Consent	X								
Medical history; Diagnosis[1]	X								
Physical exam	X	X	X	X	X	X		D30	
Vital signs, ECOG Performance status[2]	X	X	X	X	X	X		D30	
AEs & concomitant medications	X	X	X	X	X	X	X[12]	X	
Drug compliance review (entinostat)			X	X	X	X	X[12]	D30	
LABORATORY ASSESSMENTS									
Complete Blood Cell Count w/ diff (CBC)	X	X[11]	X	X	X	X	X[12]	D30	
Comprehensive Metabolic Profile (CMP)	X	X[11]	X	X	X	X	X[12]	D30	
Magnesium, Phosphate, Uric Acid, Lactate Dehydrogenase	X	X[11]	X	X	X	X	X[12]	D30	
PT/INR and aPTT	X								
Thyroid Function (TSH, T4, free T3)[3]	X		X		X	Q3cycles			
Pregnancy test WOCBP[4]	X	X							
DISEASE ASSESSMENT									
CT of chest, abdomen and pelvis[5]	X			X		X[5]		D30[5]	Per SOC
Bone scan[5]	X			X		X[5]		D30[5]	Per SOC
MRI of brain[5]	X								
TREATMENT EXPOSURE									
Entinostat		D1,8,15	D1,8,15	D1,8,15	D1,8,15	D1, 8, 15, 22			
Nivolumab		X	X	X	X	X	X[12]		
Ipilimumab		X	X	X	X				
CORRELATIVE STUDIES									
Archival Tissue (required if available)[6]	X								
Optional fresh biopsy[6]	X		X						
Blood samples[7]		X	X		X	Q2 cycle[7]			

	Screen	Cycle= 21 days				Cycle= 28 days		Safety follow up[13]	Long-term Follow up[14]
	-28 days[1]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5+		30/100 days (±7)	Q 6 months (±30)
		D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D15 ±3[12]		
BANKING SAMPLES									
Whole Blood[8]		X							
Unstained Slides (if available)[9]		X							
Serum and Plasma[10]		X						D30	
FOLLOW-UP									
Survival status, subsequent therapy									X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1: Medical History; other data to obtained during this assessment includes: diagnosis and staging to include pathology report and staging documentation. a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented.

2: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status.

3: Thyroid function to be checked at screening, Cycle 2 Day 1, Cycle 4 Day 1, then every 3rd cycle thereafter starting with Cycle 6. More frequent testing is at the discretion of the site investigator. TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator.

4: For women of childbearing potential (WOCBP): serum pregnancy test during screening and a urine pregnancy test within 3 days prior to first dose of study drugs. If the screening serum test was done within 3 days prior to receiving the first dose of study drugs, a urine test is not required.

5: Tumor response assessment will be performed at screening, prior to Cycle 3 Day 1 then prior to Cycle 5 (±7); Tumor imaging to be performed every 8-12 weeks after Cycle 5 based on investigator discretion. Tumor imaging to be done at treatment discontinuation at discretion of investigator. Baseline bone scan will be obtained if there is any suspicion of metastatic bone involvement. If bone scan is positive at baseline, it will be included with subsequent tumor response assessments as noted above at the discretion of the treating physician. MRI of brain should be performed at screening only to evaluate for the presence of brain metastases. Additional imaging of the brain will be at the discretion of the treating physician. Tumor imaging modality used should be consistent throughout trial.

6: Archival tissue from a metastatic lesion or nephrectomy (metastatic lesion preferred) is required if available and will be obtained at screening. If archival tissue is unavailable, patients will be given the option to consent to a biopsy during the screening phase prior to Cycle 1 Day 1 treatment. All subjects with accessible tumor will be given the option to consent to a second optional biopsy on Cycle 2 Day 1. The Cycle 2 Day 1 samples will be collected ~2 hours following the most recent dose of entinostat. To ensure that these samples are obtained at the correct time, patients are urged to take their entinostat dose in the clinic on the day of on-treatment sample collection. The time of the entinostat dose and the time of sample collection must be recorded.

7: Serial blood samples for PBMCs and plasma, serum will be collected prior to treatment Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, and then every 2nd cycle thereafter starting with Cycle 6.

8: Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

9: Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

10: Serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.

11: If screening (baseline) CBC and CMP (including Mg, Phos, uric acid and LDH) were performed within 7 days of Day 1 of treatment, these do not need to be repeated. All laboratory assessments should be done prior to treatment.

12: During maintenance, subjects will receive nivolumab IV over 30 minutes at 480 mg on Day 1 of each cycle. Subjects that do not tolerate every 4 week dosing regimen may receive nivolumab 240 mg IV over 30 minutes on Day 1 and Day 15 of each cycle. Those subjects receiving nivolumab on Day 15 will have laboratory testing as well as AE and conmed assessment. These subjects will continue every 2 week dosing for the remainder of study treatment.

13: A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. AEs will be collected for 100 days after the end of treatment. This may be accomplished via phone call, email or medical records.

14: Subjects who discontinue treatment for any reason will be followed every 6 months until death, withdrawal of consent, or the end of the study, whichever occurs first. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Correlative blood and fresh tissue studies will be analyzed at Indiana University. Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.1 Tissue

Missed biopsies will not be considered protocol deviations for the purposes of this study.

8.1.1 Tissue at Screening

Archival tissue from a metastatic lesion or nephrectomy (metastatic lesion preferred) is required if available and will be obtained at screening after eligibility is reviewed. If archival tissue is unavailable, patients will be given the option to consent to a biopsy during the screening phase prior to treatment. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression.

- Tumor tissue suitable for PD-L1 expression testing should be of good quality based on total and viable tumor content. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
- Acceptable samples include core needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

8.1.2 Fresh Tissue Cycle 2 Day 1

All subjects with accessible tumor will be given the option to consent to a second, optional biopsy during Cycle 2 on Day 1 (±7 days). Screening and Cycle 2 Day 1 tumor biopsy samples for gene expression analysis will be collected from patients who consent and who have accessible tumor per institutional procedures. The biopsy sample will be split into two portions: one (1) portion will be placed in RNAlaterTM and one (1) portion will be placed in 10% formalin solution.

The Cycle 2 Day 1 samples will be collected ~2 hours following the most recent dose of entinostat. To ensure that these samples are obtained at the correct time, patients are urged to take their entinostat dose in the clinic on the day of on-treatment sample collection. The time of the entinostat dose and the time of sample collection must be recorded.

Biomarker assays will be done by IHC to examine:

- PDL-1/2
- T effector cells
- Tregs
- MDSCs
- M1/M2 macrophages

8.2 Peripheral Blood Samples

8.2.1 Whole Blood

Serial blood samples for PBMCs and plasma, serum will be collected during prior to treatment C1D1, Cycle 2 Day 1, Cycle 4 Day 1, and then every 2nd cycle thereafter starting with Cycle 6. Blood samples should be collected prior to treatment administration whenever possible. Biomarker assays will be done to examine:

- CD45 cells
- Effector CD4 T cells
- Effector CD8 T cells
- FoxP3+ CD4+ Regulatory T cells (Tregs)
- CD11b+ CD14+ HLA-DR low/neg MDSCs
- Circulating microRNAs

8.3 Samples for future studies

Subject consent will be obtained for additional samples collected for future unspecified cancer related research. Hoosier Cancer Research Network will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.4 Storage of Biospecimens

Any specimens remaining (leftover) once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research. Permission for storage of leftover samples will be obtained from subjects during informed consent.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

Response assessments will be made both using the Immune Related Response Criteria (irRC) and using RECIST v1.1, allowing additional comparisons among these criteria for disease response assessment. The same measurable and non-measurable lesions will be followed by both RECIST v1.1 & irRC. Disease progression will be determined using RECIST 1.1 criteria.

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.4 Progression Free Survival
A measurement from the date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.5 Overall Survival

Overall survival is defined by the date of treatment start to date of death from any cause.

9.9 Immune Related Response Criteria (irRC)

This study will evaluate concordance of the Immune Related Response Criteria (irRC) with RECIST 1.1. These response criteria were developed to overcome the variable and unusual patterns of response to immunotherapeutic agents, in particular, ipilimumab. The development of the guidelines was prompted by observations, mostly in subjects with metastatic melanoma, of initial disease progression followed by later response, late responses, and mixed responses with an overall decrease in tumor burden. See article in Clin Cancer Res 2009;15(23) December 1, 2009.

9.9.1 Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Table: Comparison of WHO and irRC criteria

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, non measurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

9.9.2 Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRC response categories have been modified from those of WHO criteria as detailed in the above table.

9.9.3 Overall response using the irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR)**: Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR)**: Decrease, relative to baseline, of 50% or greater in the sum of the products of the 2 largest perpendicular diameters of all *index* and all new measurable lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable
- **Disease (irSD)**: Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD)**: At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC New lesions in and by themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD, which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

9.9.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria (see Table below):

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.

- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
    - At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions.
    - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.
- **Immune-Related Best Overall Response Using irRC (irBOR)** irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Derivation of irRC overall responses

Measurable Response	Nonmeasurable Response		Overall Response
Index and new, measurable lesions (tumor burden),*%	Non-index lesions	New, Nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal Progression	Any	irPR†
↓≥50	Any/Stable	Any	irPR†
↓≥50	Unequivocal Progression	Any	irPR†
↓<50 to <25↑	Any/Stable	Any	irSD
↓<50 to <25↑	Unequivocal Progression	Any	irSD
≥25	Any	Any	irPD†
*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only. †Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.			

10. DRUG INFORMATION

Please refer to the current versions of the Investigator's Brochures (IBs) for additional information regarding these drugs.

10.1 Entinostat

Entinostat is a synthetic orally available HDACi that belongs to the class of substituted pyridylcarbamates. Entinostat is in the pharmacologic class of antineoplastic agents.

10.1.1 Supplier/How Supplied

Syndax will supply entinostat at no charge to subjects participating in this clinical trial.

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 investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Storage and Stability

Entinostat is an oral drug supplied by Syndax as pink to light red (1 mg) or yellow (5 mg) as polymorph B coated tablets. Each tablet contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate as inert fillers. The film coating consists of hypromellose, talc, titanium dioxide, and ferric oxide pigments (red and yellow) as colorants. Entinostat 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 and not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC). The pharmacist should dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers.

10.1.3 Dispensing

Entinostat must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Entinostat should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.4 Adverse Events

Please refer to the entinostat Investigator's Brochure for a complete list of adverse events. Entinostat has been evaluated as monotherapy and in combination with other agents in greater than 1055 cancer patients in 31 clinical studies sponsored by Syndax or predecessors, the United States NCI and KHK, of which 8 are active.

Across indications and regimens, the AEs reported most commonly in entinostat-treated patients include:

- Fatigue (63%)
- GI disturbances, primarily nausea (55%), vomiting (32%), anorexia (31%), and diarrhea (32%)
- Hematologic abnormalities, including anemia (47%), thrombocytopenia (41%), neutropenia (33%), and leukopenia (31%)

Fatigue is the most common AE associated with entinostat. In placebo-controlled study SNDX-275-0301, the incidence of fatigue of any grade was 48% versus 26% for entinostat versus placebo, with the incidence of Grade 3 or 4 fatigue being 13% vs 3%. Fatigue tended to occur early and to be variable in duration, with some patients experiencing short durations and others experiencing prolonged fatigue

over several months. Fatigue was often, but not always accompanied by anemia, which also was more prevalent in the entinostat group relative to placebo. Overall, fatigue was tolerable.

Neutropenia has been associated commonly with entinostat. In placebo-controlled study SNDX-275-0301, the incidence of neutropenia of any grade was 30% vs 0% for entinostat vs placebo, and approximately half of the events were Grade 3. Neutropenia tended to occur later in treatment and in patients with disease in the bone, but was not complicated by fever or infection in this study.

The incidence of thrombocytopenia (all severities) varied markedly across entinostat studies, with incidences as high as 79% in the combination study with AZA in hematologic malignancies and as low as 15% in the combination study with the EGFR inhibitor erlotinib in solid tumors. The incidence of Grade 3 or 4 thrombocytopenia was even more disparate, with incidences of 78% in the former study and 3% in the latter. The incidence of Grade 3 or 4 thrombocytopenia was 1% in patients with solid tumors who received entinostat in combination with AZA. In monotherapy studies, the incidence of thrombocytopenia of any grade was moderately higher in hematologic malignancies relative to solid tumors (52% vs 41%, respectively), but the incidence of Grade 3 or 4 thrombocytopenia was markedly higher (46% vs 5%). Although thrombocytopenia tended to be higher in the monotherapy studies in general, this may have been due to the Phase 1 nature of these studies, which tended to enroll more heavily pretreated patients than the later-phase combination studies and which enrolled patients at doses higher than the MTD. In summary, thrombocytopenia tended to be more common and more severe in patients with hematologic malignancies (who typically have compromised bone marrow and/or preexisting thrombocytopenia) compared to patients with solid tumors and was higher with certain drug combinations (i.e., AZA). Thrombocytopenia is considered a class effect of HDACi and appears to be due to an effect on platelet maturation and release as opposed to myelosuppression, a cytotoxic effect on megakaryocytes, or a decrease in the half-life of circulating platelets (Bishton 2011).

Entinostat Combination Therapy
Overall, the AE profile of entinostat when given in combination was similar to that seen when given as monotherapy, with the most commonly reported AEs (regardless of tumor type) being fatigue (68%), nausea (59%), anemia (49%), thrombocytopenia (40%), leukopenia (35%), diarrhea (35%), neutropenia (34%), and vomiting (34%).

As would be expected, the AE profiles of entinostat when given in combination varied somewhat based on the combination agent and the corresponding patient population. Higher rates of AEs overall and of individual AEs were seen when entinostat was given with AZA than when given in combination with an AI. Consistent with the overall AE profile of entinostat, nausea, vomiting, fatigue, and anemia were common regardless of the combination agent.

When given in combination with AIs in patients with breast cancer, the individual AEs and Grade 3 or 4 AEs occurred less frequently compared to other patient populations and regimens. Overall, the AEs reported most frequently in this setting were fatigue (50%), nausea (45%), diarrhea (27%), peripheral edema (25%), neutropenia (24%), and vomiting and weight decreased (each 23%). The overall incidence of Grade 3 or 4 AEs was 55%; however, the incidence of individual Grade 3 or 4 AEs was relatively low, with the only events occurring at an incidence >5% being neutropenia (13%) and fatigue (9%). In the placebo-controlled study SNDX-275-0301, in which entinostat was given in combination with the AI exemestane, Grade 2 or greater fatigue occurred early in treatment (C1 or 2). The duration of fatigue

was variable, with some patients experiencing multiple short episodes, and others prolonged fatigue that persisted for several months. For some patients, dose modification was helpful in ameliorating fatigue. Fatigue was accompanied in some cases by anemia, which also was more prevalent in the entinostat group compared with placebo. Only 1 patient treated with entinostat permanently discontinued treatment due to fatigue. In the same study, neutropenia was also a notable treatment-emergent AE, tending to occur later in treatment and in patients with disease involvement in the bone. Approximately half of the patients with neutropenia required a dose modification; treatment was discontinued due to neutropenia in only 1 entinostat-treated patient. Importantly, the neutropenia was not associated with fever or infection.

Overall, among the 535 patients with solid tumors receiving entinostat in combination, the AEs reported most frequently were: fatigue (66%), nausea (58%), anemia (44%), vomiting and diarrhea (each 34%), thrombocytopenia and anorexia (each 30%), leukopenia (25%), dyspnea (22%) and injection site reaction (20%).

Overall, among the 205 patients with hematologic malignancies receiving entinostat in combination, the SAEs reported most frequently were: fatigue (70%), thrombocytopenia (67%), anemia (65%), neutropenia (62%), leukopenia (60%), nausea (58%), anorexia (41%), diarrhea (29%), hypoalbuminaemia (36%), injection site reaction (35%), febrile neutropenia (34%), vomiting (33%), constipation (32%), hyperglycaemia, hypocalcaemia and hyponatraemia (each 31%), oedema peripheral and dyspnea (each 30%), and headache and hypophosphataemia (each 20%).

10.2 Ipilimumab

Ipilimumab (BMS-734016, MDX-010) is a recombinant, human monoclonal antibody that binds to the CTLA-4. Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

10.2.1 Supplier/How Supplied

Bristol-Meyers Squibb will supply ipilimumab at no charge to subjects participating in this clinical trial.

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

A copy of the drug destruction certificate should be maintained for provision to BMS at the end of the study.

10.2.2 Product Description and Dosage Form

Ipilimumab injection, or 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab injection, 200 mg/40 mL, is supplied in 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

10.2.3 Storage and Stability

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

After opening:
Solution for infusion: From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hrs at 25°C and 2 to 8°C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2°C to 8°C) or at room temperature (20°C to 25°C).

10.2.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused ipilimumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Dispensing

Ipilimumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Ipilimumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.2.6 Administration

Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non-PVC/non-di-(2-ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 and 4 mg/mL and stored in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 μm). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to

assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

10.2.7 Adverse Events

Please refer to the ipilimumab Investigator's Brochure for a complete list of adverse events.

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, with the potential for clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (eg, hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (eg, uveitis/episcleritis). The majority of these inflammatory AEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. The majority of the inflammatory AEs is reversible with the guidance issued below and in Appendix 2. In rare cases, these inflammatory AEs may be fatal.

Gastrointestinal Toxicities

The most common site for ipilimumab-induced GI toxicity was the lower GI tract, and the most common presentation was mild to severe diarrhea or colitis with occasional bloody stools. In some cases, diarrhea began as mild and then worsened. Constipation was rarely associated with ipilimumab administration.

Liver Toxicities

Subjects receiving ipilimumab may develop elevations in LFTs in the absence of clinical symptoms. Occasionally, patients may present with symptoms, including right upper quadrant abdominal pain or unexplained vomiting.

Endocrine Toxicities

The most common inflammatory endocrine toxicities occurring in ipilimumab-treated subjects are hypophysitis and hypopituitarism. Secondary cortisol deficiency (hypoadrenalism), hypothyroidism or thyroiditis, and, less commonly, other endocrinopathies may occur concomitantly with hypophysitis; however, these may also present as the only or as primary endocrinopathy. Most patients with hypopituitarism presented with nonspecific complaints such as fatigue, visual field defects, confusion, or impotence. Some patients have had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low ACTH and cortisol were the most common biochemical abnormality; abnormal (mostly low) thyroid-stimulating hormone (TSH), free thyroxine (fT4), triiodothyronine (T3), testosterone, or prolactin have also been reported in some subjects.

Skin Toxicities

The most common inflammatory skin toxicities occurring in ipilimumab-treated subjects are rash and pruritus, mostly mild to moderate in severity. Two cases of fatal treatment-related toxic epidermal necrolysis have been reported in clinical trials. Postmarketing surveillance identified a fatal toxic epidermal necrolysis event in 1 subject who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy. Caution should be used when considering the use of ipilimumab in patients who have previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy.

Neurological Toxicities
Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (eg, tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and noninflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded.

Other Toxicities
Ocular inflammation, manifested as Grade 2 or 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms.

Other presumed inflammatory events reported include, but were not limited to, the following (individually reported for < 1% of subjects unless noted otherwise): arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, eosinophilia, pericarditis, urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, infusion reactions, and MG.

10.3 Nivolumab
Nivolumab (ONO-4538, MDX-1106, BMS-936558-01 or BMS-936558) is an anti-PD-1, anti-programmed cell death-1 monoclonal antibody.

10.3.1 Supplier/How Supplied
Bristol-Meyers Squibb will supply nivolumab at no charge to subjects participating in this clinical trial.

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

A copy of the drug destruction certificate should be maintained for provision to BMS at the end of the study

10.3.2 Product Description and Dosage Form
Nivolumab Injection, 100mg/10 mL (10mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

10.3.3 Storage and Stability
Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. For

additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions."

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

10.3.4 Dispensing
Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Nivolumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.3.5 Administration
Nivolumab is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

10.3.6 Adverse Events
Please refer to the nivolumab Investigator's Brochure for a complete list of adverse events.

Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized below. Management algorithms are found in Appendix 2.

The overall safety experience with nivolumab is based on experience in approximately 12,300 subjects as either monotherapy or in combination with other therapeutics. In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. Select AE categories group together the most common and impactful PTs by

organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs.

Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.

Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

Diverticular Perforation

The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis [36, 37]. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation [38]. Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced liver injury (DILI) have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

Endocrinopathies
Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Skin Adverse Events
Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Renal Adverse Events
Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of renal cell carcinoma or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

Neurologic Adverse Events
Neurologic AEs have been uncommonly observed following treatment with nivolumab. The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination.

Infusion Reactions
Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab.

Lipase/Amylase Elevations
Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and

elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (e.g., abdominal pain) or radiographic findings (e.g., stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values.

Uveitis and Visual Complaints
Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with the sponsor-investigator should be sought for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Other Immune-mediated Adverse Events
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to BMS

HCRN will report all SAEs to BMS **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to BMS as it is received from site.

Contact information for sending SAE information to BMS:
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

Reconciliation with the BMS safety database should occur every 3 months and prior to the database lock or final data summary. To complete the reconciliation, the sponsor-investigator or designee will request from BMS GPV&E (aepbusinessprocess@bms.com) the SAE reconciliation report. The request will include a reference to the study specific BMS protocol number. BMS GPV&E will send the sponsor-investigator or designee the SAE reconciliation report to verify and confirm that all SAEs have been transmitted to BMS GPV&E. If the sponsor-investigator or designee determines a SAE was not submitted to BMS, the case should be sent immediately to BMS Worldwide Safety (worldwide.safety@bms.com). The data elements listed on the GPV&E SAE reconciliation report will be used for case identification purposes.

11.2.2.3 HCRN Requirements for Reporting SAEs to Syndax

HCRN will report SAEs to Syndax within **1 business day** of receipt of the SAE Reporting Form from a site. Follow-up information will be provided to Syndax as it is received from a site.

Contact information for sending SAE information to Syndax:
Email Address: SyndaxSAEReporting@syndax.com
Facsimile Number: 1-888-529-3580

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the BMS and Syndax's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to BMS and Syndax at the time of submission to FDA.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to BMS and Syndax at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to this Trial

BMS and Syndax will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol; however, all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outline below.

12.1 Study Design

This is an open-label Phase II clinical trial with a safety lead-in. No randomization or blinding is involved.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

Overall Response rate (ORR) per RECIST is defined as CR plus PR by RECIST 1.1.

12.2.2 Definition of Secondary Endpoints

Overall Response rate per irRC is defined as irCR plus irPR as per irRC. PFS per RECIST is defined as the time from treatment start until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause. PFS per irRC is defined as the time from treatment start until the criteria for disease progression is met as defined by irRC or death as a result of any cause. Censoring will occur at date of last disease evaluation. Overall survival will be defined as the time from treatment start until death from any cause. Censoring will occur at last known date alive.

Adverse events will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

12.3 Sample Size and Accrual

For the safety Lead-In, up to 18 subjects may be enrolled. For Phase II, assuming a type I error rate of 5% and a power of 90% to compare an uninteresting overall response rate (per RECIST 1.1) of 5% while declaring efficacy at 20%, Simon's optimal two stage design enrolls 21 patients in the first stage (with 6 of the 21 from the Safety Lead-in RP2D cohort). If at most one response is seen, then the trial is terminated for futility. Otherwise, stage 2 accrual continues to a total of 41 patients. If at most 4 patients respond among the 41 patients, the combination would not warrant further investigation. If at least 5 patients respond, this therapy would warrant further investigation. The average sample size is 26.66 and the early termination probability is 71.70% for a drug with a response rate of 5%. All the calculations are based on the R function ph2simon from the package clinfun.

Due to Funder decision, enrollment will halt after completion of accrual to the safety lead in group and not move on to Phase II. This decision is a result of a shift in priorities at the Funder level and not due to safety issues. Subjects currently on treatment will continue until the criteria for treatment discontinuation as defined above is met.

12.4 Population for Analysis

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise of all subjects that take a least one dose of study drug.

12.5 Assessment of Safety

Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

12.6 Assessment of Efficacy

ORR and PFS will be assessed with RECIST 1.1 and irRC.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

For the Phase II study, the primary endpoint of objective response rate (per RECIST) in all evaluable and eligible patients will be summarized with the point estimate and corresponding 95% confidence interval that accounts the nature of two-stage design (Jung SH and Kim KM. On the estimation of the binomial probability in multistage clinical trials. Statistics in Medicine 23, 881-896. 2004). As an exploratory analysis, this will be also done separately for the patient cohort defined by their previous treatment, either nivolumab plus ipilimumab or nivolumab alone, respectively.

12.7.2 Analysis Plans for Secondary Objectives

Safety will be assessed in the Safety population. Separate frequency tables will be generated for the safety run-in (by cohort) and the Phase II study. ORR by irRC will be analyzed similarly to the primary endpoint. Progression free (by both RECIST and irRC) and overall survival will be estimated using standard Kaplan-Meier curves. The median time-to-event for survival endpoint will be estimated along with the corresponding 95% confidence interval. Similar to Section 12.7.1, the analysis will be first done for all evaluable and eligible patients, and then done separately for the nivolumab plus ipilimumab cohort and the nivolumab alone cohort.

12.7.3 Analysis Plans for Exploratory Objectives

Quantitative analysis of correlative endpoints will be characterized by their mean and corresponding 95% confidence interval by time point. Changes over time in PD-L1/L2 expression levels in tumor and blood, microRNA, and immune markers (see Section 8 for details) will be analyzed with paired t-tests. Correlations with clinical outcomes will be examined using logistic and Cox regression models. Similar

to Section 12.7.1, the analysis will be first done for all evaluable and eligible patients, and then stratified for their previous treatment (nivolumab plus ipilimumab vs nivolumab alone) in the analysis using the logistic and Cox regression models.

12.8 Interim Analysis/Criteria for Stopping Study

The formal interim analysis for efficacy is described in Section 12.3.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for High Risk Safety Lead-In/Phase II Trials.

HCRN facilitated oversight activities for High Risk Safety Lead-In/Phase II Trials include:

- Review and processing of all AEs requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data.
- Investigators will conduct continuous review of data and patient safety. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify HCRN who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety.
- Coordinate, during safety lead-in, *weekly* (Phase I) meetings (Safety Calls),and subsequently, during the phase II portion, *monthly* (Phase II) meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

The IUSCC DSMC will review study data semi-annually during the active treatment and safety follow-up portion of the trial per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, HCRN will provide the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping/decision rules described in study design
- HCRN weekly (Phase I) or monthly (Phase II) study update meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator (SI) and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the study reports.

13.2.1 DSMC DLT Review

Prior to making dose escalation/expansion/de-escalation decisions, the SI and the study team will officially review all toxicity events for each subject for confirming treatment-related DLT. The study statistician will assist the determination of DLT and the interpretation of the statistical rule for dose escalation. Once a decision has been reached by the investigator, the official decision and toxicity data will be submitted to the DSMC via email (IUSCC-DLT-Review-L@list.iupui.edu). Treating additional subjects may not proceed until official DSMC correspondence confirms approval of dosing decisions for the next stage.

13.2.2 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.4 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

13.4.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. During onsite monitoring visits, source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits

or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial sites may also be subject to quality assurance audit by BMS, Syndax or its designee as well as inspection by appropriate regulatory agencies.

13.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, BMS, Syndax, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16 REFERENCES

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6. Shen L, Ciesielski M, Ramakrishnan S, Miles KM, Ellis L, Sotomayor P, Shrikant P, Fenstermaker R, Pili R. Class I histone deacetylase inhibitor entinostat suppresses regulatory T cells and enhances immunotherapies in renal and prostate cancer models. PLoS One. 2012 Jan 27;7(1):e30815.
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8. Shen L, Orillion A, Pili R. Histone deacetylase inhibitors as immunomodulators in cancer therapeutics. Epigenomics. 2016 Mar;8(3):415-28.
9. Pili R, Shen L, George S, Hammers H, Sandecki A, Collins C, Espinoza-Delgado I, Carducci MA. Phase I/II study of high-dose interleukin 2, aldesleukin, in combination with the histone deacetylase inhibitor entinostat in patients with metastatic renal cell carcinoma. ASCO 2016.

11. APPENDICES

11.1 Appendix 1. Concomitant Medications to Avoid

Examples of sensitive *in vivo* CYP substrates and CYP substrates with narrow therapeutic range are summarized below.

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[3], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[3]

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.

P-gp Inhibitors and Inducers

Inhibitors	Inducers
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

Gastric Acid Reducing Drugs

Proton Pump Inhibitors	• Omeprazole (Prilosec, Zegerid) • Lansoprazole (Prevacid) • Rabeprazole (AcipHex) • Pantoprazole (Protonix) • Esomeprazole (Nexium)
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

Information obtained from the following website: Gastric acid reducing drugs: http://www.everydayhealth.com/ulcer/ulcer-treatment.aspx

11.2 Appendix 2. Nivolumab and Ipilimumab Adverse Event Management Algorithms

These general guidelines constitute guidance to the site Investigator and may be supplemented through discussions with the Sponsor-Investigator by contacting the BTCRC project manager. The guidance applies to all immuno-oncology agents and regimens.

As general principle, differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

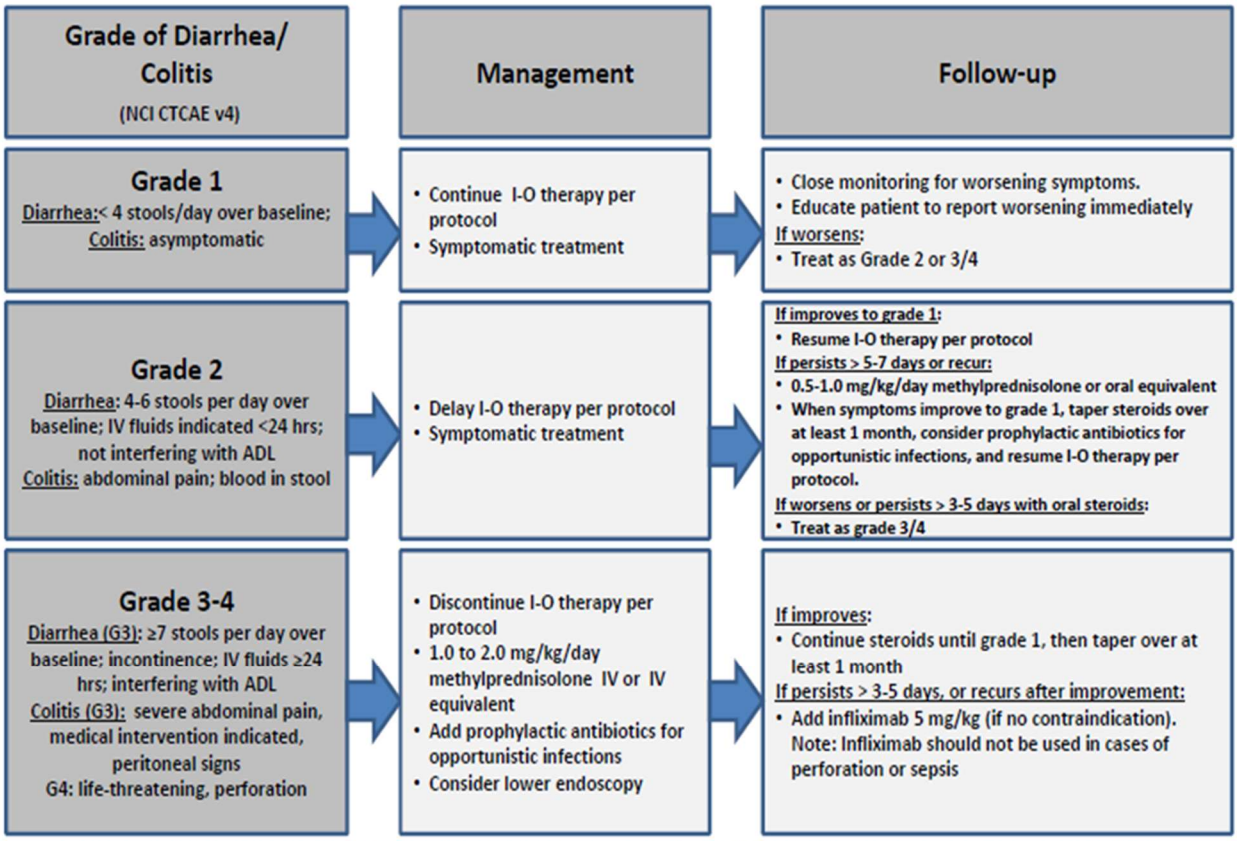
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

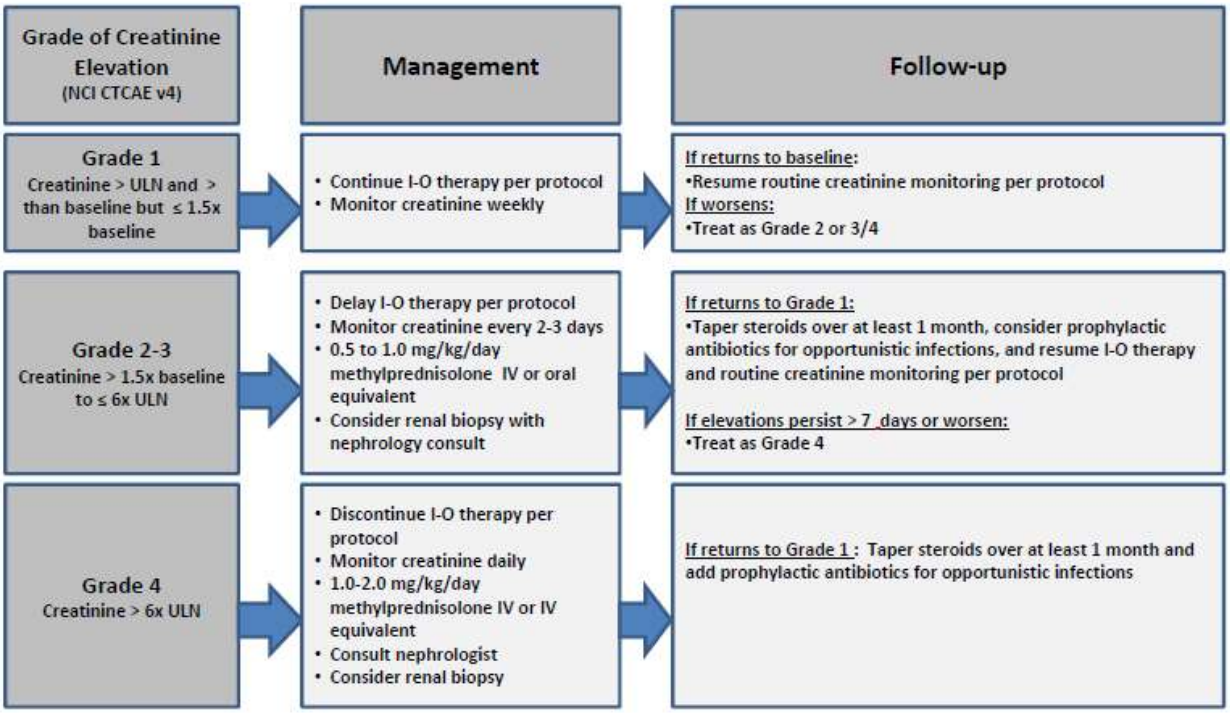


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

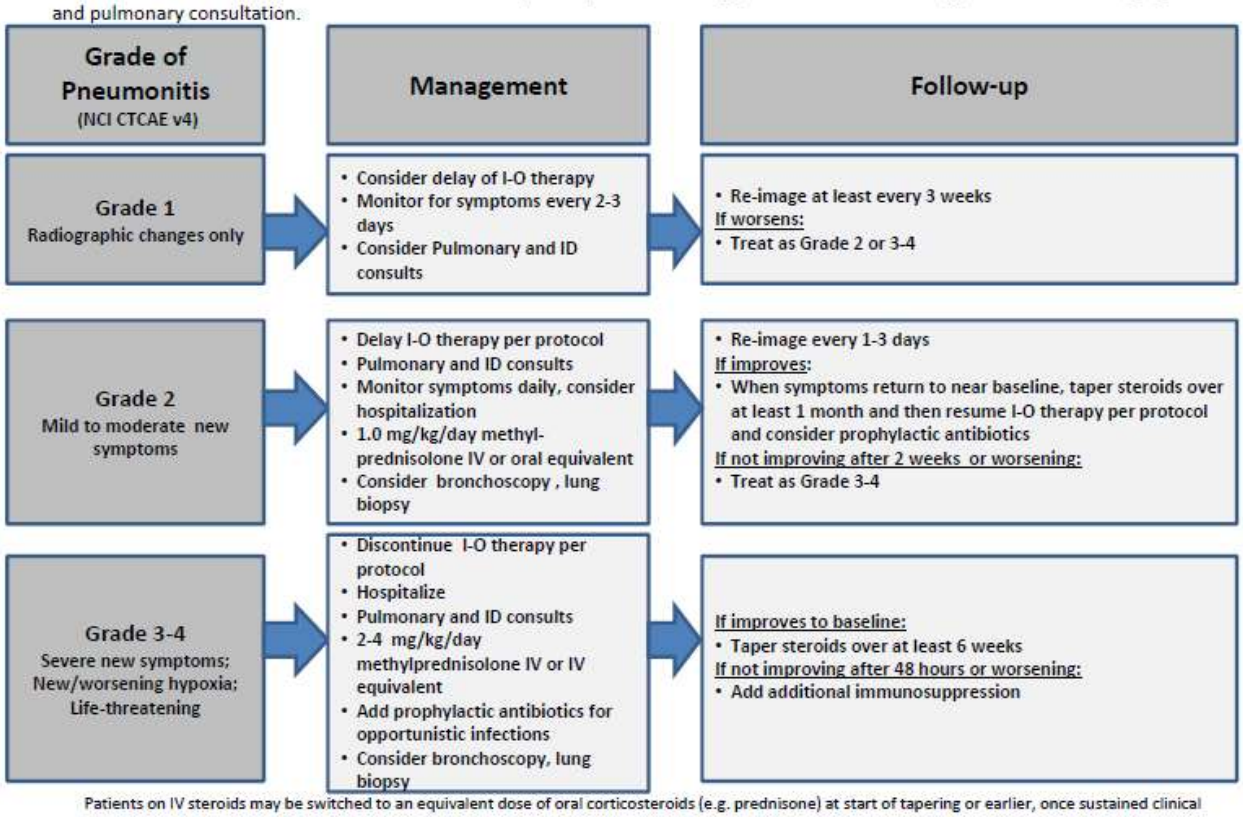


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

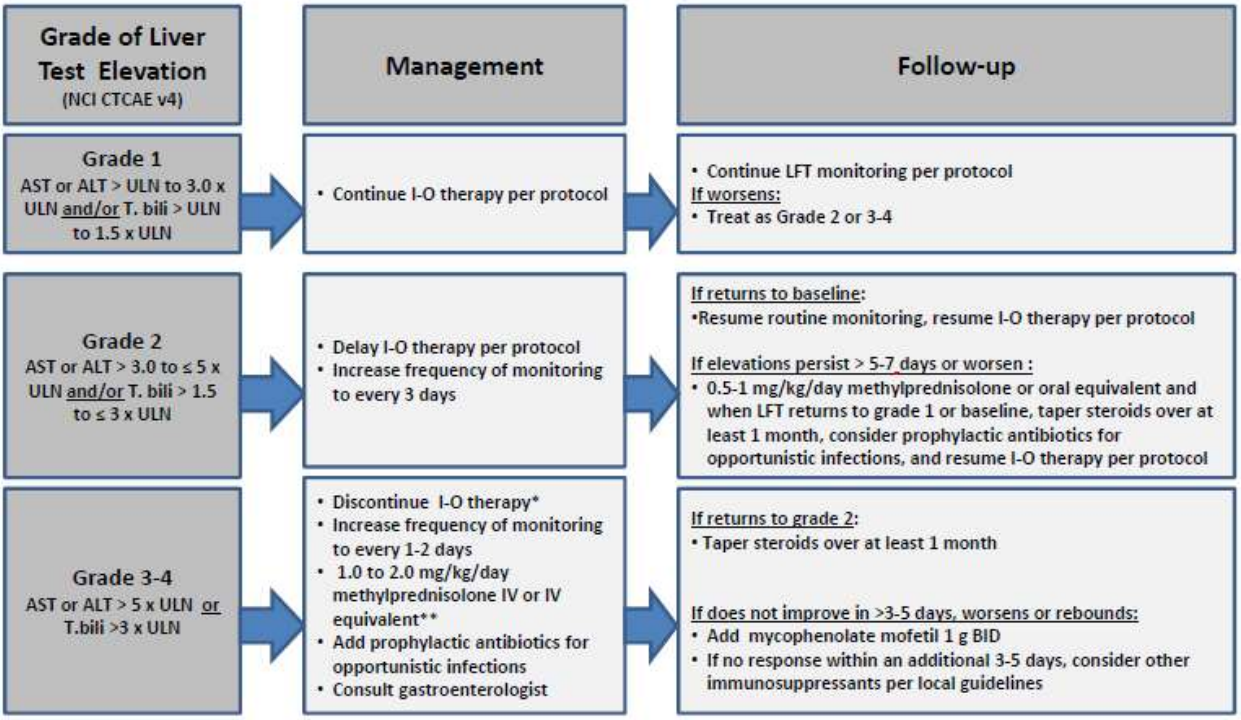


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

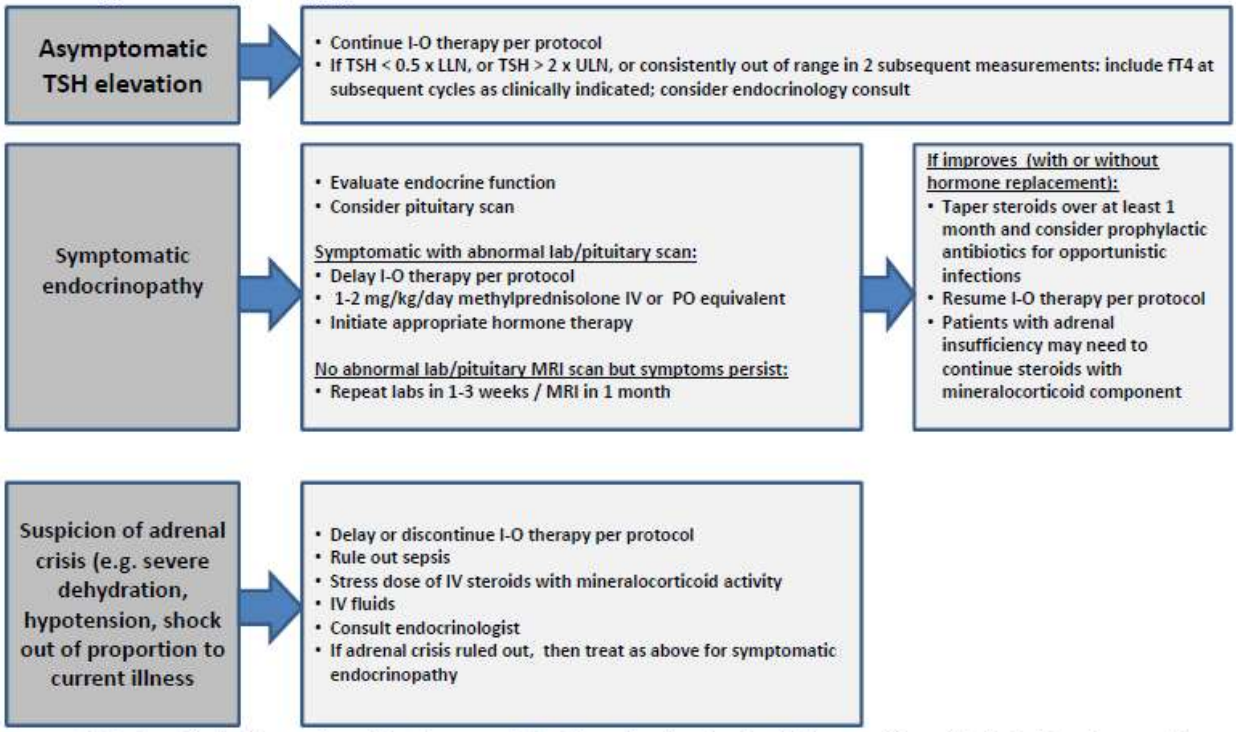
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

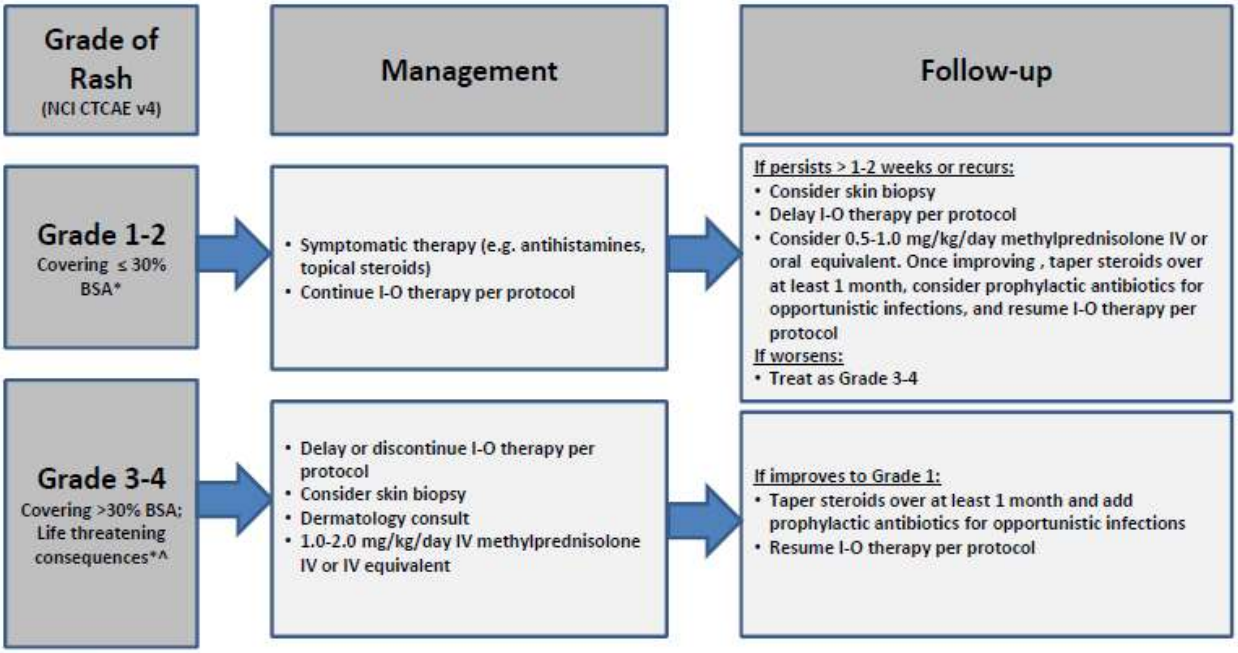


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

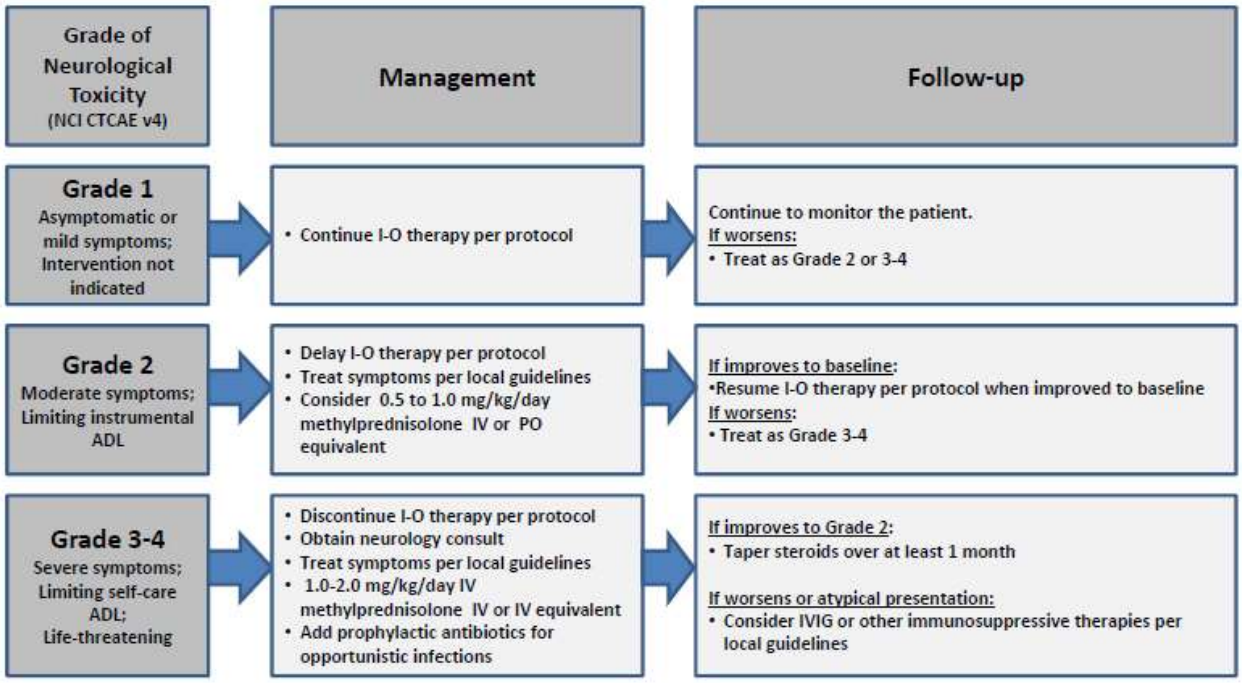


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

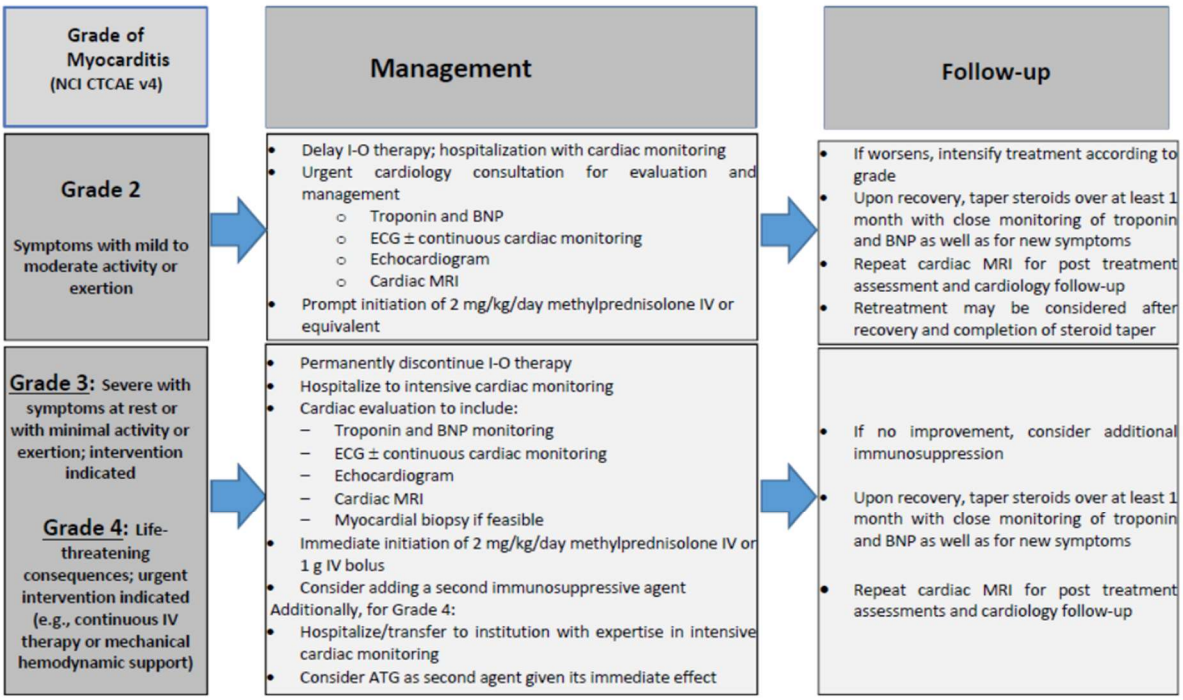
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging