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TITLE: A Phase II Study of Epigenetic Therapy with Azacitidine and Entinostat with Concurrent Nivolumab in Subjects with Metastatic Non-Small Cell Lung Cancer.

Center: Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center

Principal Investigator:
Name Julie Brahmer, MD
Telephone 410-502-7159
Fax 410-614-9334
e-mail brahmju@jhmi.edu

Participating Institutions: Norris Comprehensive Cancer Center, University of Southern California; University of Pittsburgh Medical Center

USC Principal Investigator: Jorge Nieva, MD, Jorge.Nieva@med.usc.edu
1441 Eastlake Avenue, Room 3440
Los Angeles, CA 90089-2211

LAC+USC Medical Center
USC Sub-Site Principal Investigator Jorge Nieva, MD
328-865-0421
1200 N. State St.
Los Angeles, CA 90033

Keck Medical Center of USC Pasadena
USC Sub-Site Principal Investigator Jorge Nieva, MD
328-865-0421
625 S. Fair Oaks Ave, #400,
Pasadena, CA 91105

USC Norris Oncology/Hematology-Newport Beach
USC Sub-Site Principal Investigator Jorge Nieva, MD
323-865-0241
520 Superior Avenue, Suite 300
Newport Beach, CA 92663

Johns Hopkins Bayview Medical Center
BV Lead Site Co-Investigator: Julie Brahmer, MD
4940 Eastern Avenue
Baltimore, MD 21224

Sibley Memorial Hospital (Johns Hopkins)
Sibley Lead Site Co-Principal Investigator: Benjamin Levy, MD
Sibley Memorial Hospital
5255 Loughborough Rd. NW
Washington DC 20016

University of Pittsburgh Medical Center Lung Cancer Center of Excellence
UPMC Principal Investigator: James G. Herman, MD
hermanj3@upmc.edu
Cancer Pavilion
5150 Centre Avenue
Pittsburgh, PA 15232

Coordinating Center:
Lead Study Coordinator:

Name	Amber Michalik
Telephone	410-502-0756
e-mail	amichal2@jhmi.edu

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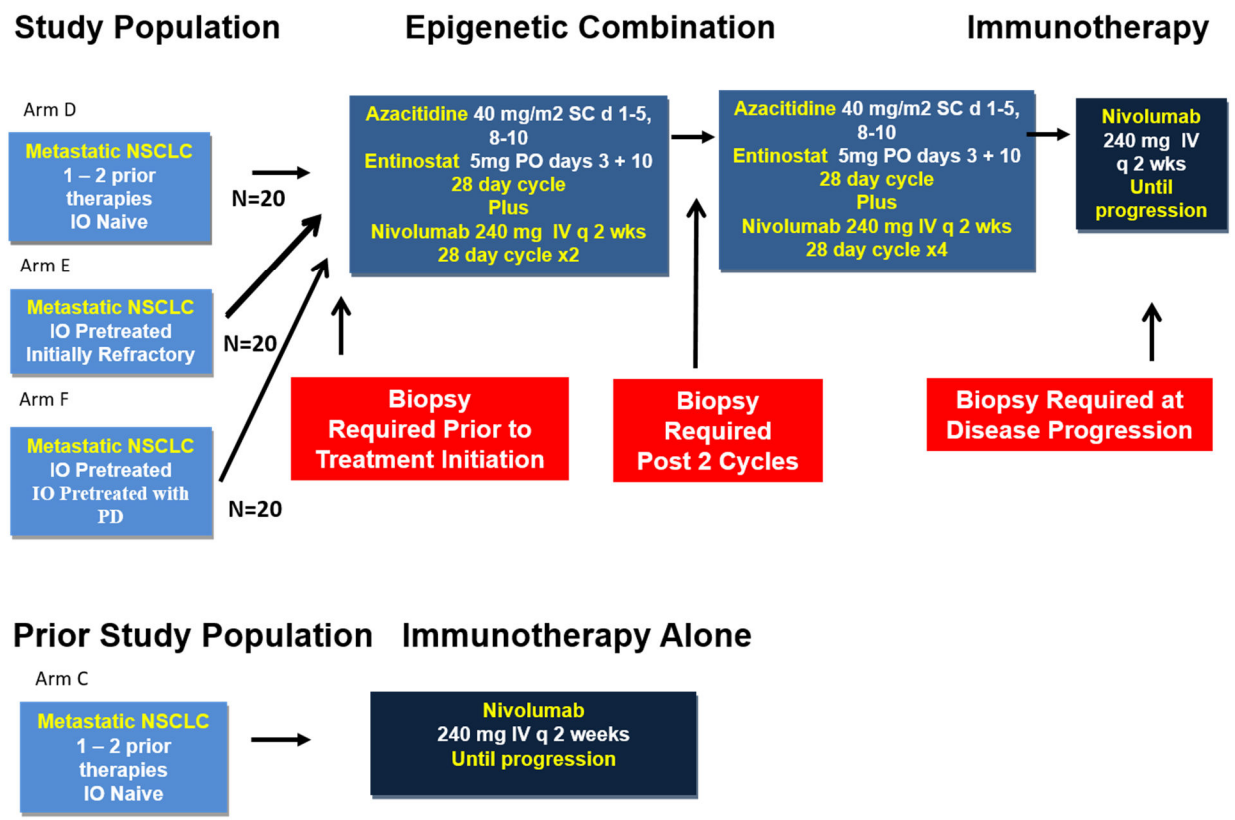
SCHEMA



- After a subject has completed 6 months of nivolumab (regardless of arm assignment), they can receive nivolumab every 4 weeks instead of every 2 weeks.

The goal of this study is to assess whether 6 cycles of concurrent epigenetic therapy consisting of azacitidine and entinostat in combination with nivolumab can increase response compared to nivolumab single agent in patients who are immunotherapy naïve (Arm D), or in patients whose disease has progressed on immunotherapy when compared to historical single agent docetaxel (Arms E & F).

Primary endpoint is the response rate by treatment Arm. Response will be assessed from first dose of trial therapy.

Patients experiencing significant toxicities on Arm D during cycles 1-6 of combination therapy of azacitidine, entinostat and Nivolumab may proceed to Nivolumab only. Otherwise, patients whose disease is responding, progressing, or stable on combination therapy with Nivolumab, azacitadine and entinostat will proceed to Nivolumab monotherapy after 6 cycles. Patients experiencing significant toxicities due to nivolumab or documented disease progression (see **Section 9**) on Arm E or Arm F during cycles 1-6 of combination therapy of azacitidine, entinostat and Nivolumab must come off study treatment. Patients whose disease is responding or stable on combination therapy with Nivolumab, azacitadine and entinostat will proceed to Nivolumab monotherapy after 6 cycles on Arms E and F.

We plan to enroll up to 20 patients each on Arms D, E and F (N=60). Allowing for up to 10% unevaluable patients, we will enroll up to 22 patients on each Arm (D-F), or a total of 66.

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1. OBJECTIVES

1.1 Primary Endpoint

1) Objective response rate
Objective response to combination Nivolumab and epigenetic therapy will be assessed by Arm. Response will be assessed by RECIST 1.1 criteria, baseline scans for this assessment will be done within 4 weeks of enrollment.

1.2 Secondary Endpoints

2) Progression free survival
Progression-free survival will be measured from the time of study enrollment until radiologic, clinical progression or death.
3) Time to Progression
Time to progression will be measured from the time treatment begins until radiologic or clinical progression is noted.
4) Overall survival
Overall survival will be measured from the time of enrollment until death.
5) Safety and tolerability
Toxicities observed in the study will be assessed by CTCAE 4.0 criteria.

1.3 Exploratory Endpoints

Assessment of tumor baseline PD-L1 expression will be performed. Serial assessment of genomic and immunologic parameters will be undertaken. Genomic analyses will include target gene DNA methylation status in circulating DNA and in pre- and post-tumor biopsies, DNA exome sequencing to assess mutational burden and status of driver gene mutations, genome wide and target gene DNA methylation levels, and RNA-seq analyses of genome wide gene expression for detection of drug induced changes in endogenous retroviral (ERV) transcripts. Assessment of immunologic parameters in pretreatment, on treatment and post-treatment (when feasible) biopsies, will also be performed and compared.

2. BACKGROUND

2.1 Lung cancer

Lung cancer is the most common cause of death from malignancy in both men and women[1]. Most non-small cell lung cancer patients present with advanced disease. Metastatic disease was typically treated with chemotherapy alone and is considered incurable with this therapy. Recently, immunotherapy has been approved in a variety of ways for the treatment of advanced lung cancer; however, many patients who receive this therapy either don't respond or develop resistance. Immunotherapy either alone or in combination with chemotherapy in the front-line treatment setting is now dominating the treatment landscape for advanced disease. Fewer and fewer patients are now receiving single agent immunotherapy in the second-line treatment setting due to the rapidly evolving treatment landscape. New, effective

therapies and strategies for lung cancer are a critical need in the immunotherapy era particularly after disease progression on first-line immunotherapy containing treatment.

2.2 Agents used

2.2.1 Azacitidine

DNA methyltransferase inhibitors have been under investigation for over 25 years. The most widely used DNA methyltransferase inhibitor is azacitidine [2]. Azacitidine is a cytidine analogue that functions as a mechanism-dependent suicide inhibitor of the DNA methyltransferase DNMT1. DNA methyltransferases recognize azacitidine as a natural cytosine. However, the azacitidine prevents the completion of the methylation reaction, leading to trapping and degradation of the DNMT1 enzyme [3]. Azacitidine is approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome[4].

2.2.2 Entinostat

Histone deacetylases (HDACs), like DNA methyltransferases, are important negative regulators of gene expression[5-7]. Several HDAC inhibitors are in active clinical development, including entinostat. In a phase I clinical trial of entinostat in 31 patients with advanced solid tumors[8], major side effects included hematologic and gastrointestinal toxicities.

2.2.3 Nivolumab

Nivolumab (BMS-936558 (MDX-1106)) is a fully human IgG4:κ monoclonal antibody that blocks PD-1, an inhibitory receptor expressed on activated T and B cells. PD-L1 or PD-L2 expressed on tumors or nontransformed cells in the tumor microenvironment can bind to PD-1 on the surface of CD4 helper and CD8 cytotoxic T cells, suppressing anti-tumor cytolytic responses[9]. Phase I testing of Nivolumab has been associated with objective responses in multiple solid tumors including non-small cell lung cancer[10-12]. BMS-936558 was generally well tolerated, with a grade 3-4 AEs in 14% of patients treated biweekly. Based on two Phase III trials showing improved overall survival when compared to single agent chemotherapy, Nivolumab has been FDA approved in the second line treatment setting of metastatic squamous and non-squamous NSCLC patients[18,19]. Trials combining Nivolumab with cytotoxic therapies, ipilimumab, and other targeted therapies in NSCLC are ongoing.

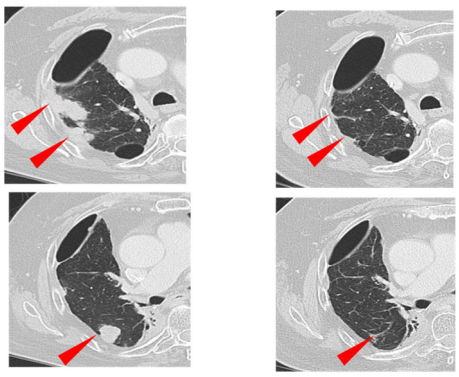
2.3 Rationale for epigenetic priming of immunotherapy

2.3.1 Azacitidine and entinostat in non-small cell lung cancer patients: the priming hypothesis

We have completed a combination study of azacitidine and entinostat in patients with extensively pretreated metastatic lung cancer[13]. This study defined a regimen of

azacitidine 40 mg/m^2 days 1-6 and 8-10 and entinostat 7 mg PO on days 3 and 10 on a 28-day schedule as safe and well-tolerated. Major objective responses were observed in 2 patients.

More surprising than the responses observed was that several patients treated on this protocol experienced major objective responses to the *subsequent* line of therapy, despite being heavily pretreated. Of 28 patients who received a subsequent line of therapy, the response rate was 29%, higher than for any agent for recurrent lung cancer (reported response rates to erlotinib, docetaxel, or pemetrexed are approximately 9%). Although the extent of data are limited, most notable of all has been the response to subsequent immunotherapy targeting the PD-1/PD-L1 pathway. Of five patients with progressive lung cancer after multiple prior therapies who were treated with azacitidine and entinostat, and who received Nivolumab or a similarly targeted anti-PD-L1 antibody(BMS-936559) as the immediate subsequent therapy, three have experienced major objective responses, a fourth has had disease stabilization beyond 6 months after initiation of Nivolumab, and the fifth has stable disease beyond 6 months but required palliative radiation to a mass eroding into the chest wall from the right lung. Of the 5 patients, two had prior radiation with concurrent chemotherapy followed by one platinum doublet, one had one prior platinum doublet, and one had two prior therapies for metastatic disease. The last patient had 4 prior therapies as well as radiation. These responses and stable disease at 24 weeks compare favorably to the 18% NSCLC response rate and a 7% stable disease rate at 24 weeks reported in the multi-dose Phase I trial of Nivolumab and 10% NSCLC response rate and 12% stable disease rate at 24 weeks reported in the multi-dose Phase I trial of BMS-936559[14,15].



Epigenetic priming? Serial CT scans of a patient with advanced NSCLC, progressive on azacitidine and entinostat, with major objective response to subsequent Nivolumab.

These responses have been quite impressive, and are ongoing; one example is shown in the figure to the right. Only one of the 5 patients was a responder to epigenetic therapy, and in fact 3 progressed at the very first time point assessed. Such major objective responses in rapidly progressing non-small cell lung cancer after multiple prior therapies are rarely observed.

2.3.2 Biological rationale

Aberrant DNA methylation and histone deacetylation represent two of the critical mechanisms of tumor-specific gene silencing. Both of these critical mechanisms of

epigenetic silencing can be reversed, using DNA methyltransferase inhibitors (such as azacitidine) and histone deacetylase inhibitors (such as entinostat). Our group has led efforts to define the biology and therapeutic implications of epigenetic gene silencing in cancer, including demonstration of synergistic re-expression of silenced tumor suppressor genes using these classes of drugs [16,17].

Beyond cell-autonomous effects, a combination of published and unpublished data offers three non-mutually exclusive mechanisms by which epigenetic modulation of tumors can enhance anti-tumor immunity. First, epigenetic modulation induces a vast array of new antigens by the tumors that are potential targets for T cell and antibody responses. Second, re-expression is induced at silenced promoters of key cytokine genes in T cells, such as interferon-gamma and IL-2 – critical effector cytokines in anti-tumor responses. Third, global demethylation of DNA in tumor cells induces a "pathogen response" pattern of gene expression, characterized in part by a type I interferon response. Specifically, in cultured NSCLC and other human cells, low doses of the DNA demethylating agent 5-azacitidine (5-Aza-CR) up-regulated pro-inflammatory, viral defense, and tumor antigen presentation pathways while increasing PD-L1 expression[18]. Colon cancer cells genetically disrupted for DNA methyltransferases (DNMT's), 5-Aza-CR targets, have a similar signature[18]. Importantly, pathways up-regulated by 5-Aza-CR, including PD-L1 expression, were found to be basally decreased in hundreds of primary SC and AC samples, including low expression and increased promoter methylation of immune -related transcription factors, prominently, *IRF7* in SC. Thus, combining epigenetic therapy with immune checkpoint blockade could significantly alter management of NSCLC[19, 20].

The very latest pre-clinical data from our group, in mouse model studies of NSCLC and serous ovarian cancer, identify that the epigenetic therapy agents generate anti-tumor responses and these, importantly are associated with immune cell infiltration, and notably activated CD8 T-cells into tumors[20, 21]. This is all associated, as outlined in the correlative science section, with an upregulation of ERV transcripts and the viral defense gene stimulation of Type 1 interferon signaling including for levels of the immune inhibitory ligand, PD-L1. These drug effects also contribute to, in tumor associated CD8 T-cells, reversion of a transcriptional profile for immune exhaustion[20]. All of these epigenetic therapy effects will predictably sensitize tumors for response to antibodies that block the PD-1 inhibitory pathway and unleash the anti-tumor immune response. Therefore, a scientific rationale underpins the combination proposed herein.

2.4 Rationale for combining epigenetic therapy with immunotherapy

2.4.1 Clinical Rationale for combination epigenetic and immunotherapies

Due to 2015 FDA-approval of nivolumab in the 2nd line treatment setting of advanced or metastatic NSCLC[22,23], this protocol was previously amended to update nivolumab administration to be given concurrently starting at the initiation of combination study treatment. Therefore, for those patients randomized to combination therapy, nivolumab will be given in combination with epigenetic therapy for 6 cycles, followed by nivolumab monotherapy until disease progression. This will provide patients treated with maximal exposure to both epigenetic therapy and the immune checkpoint inhibitor, in keeping with standard of care practice. In this manner, patients will have longer exposure to the

potential benefits of both epigenetic therapy and immune checkpoint inhibition. This update in therapy is further supported by data indicating that 58.3% (14/24) patients were unable to receive two months of epigenetic therapy alone ("priming") prior to initiation of nivolumab in an earlier therapeutic intervention in this trial (Arm A), due to both symptoms (nausea, vomiting, fatigue, pain) and subsequent rapid disease progression on epigenetic therapy alone.

Importantly, the concurrent administration of epigenetic therapy and immune checkpoint inhibition is hypothesized to quickly combine the immune attraction signals from epigenetic therapy with the initial immune-tolerance inhibiting activity of immune checkpoint blockade, and allow the patient's tumor to be exposed to this interaction for a longer and perhaps more significant length of time than in the previous treatment arm. This is supported by pre-clinical data for the combination of these agents' mechanisms of action on efficacy and overall tolerability as detailed below.

2.4.2 Biological rationale

The question of whether epigenetic therapy may be able to increase the efficacy of immune checkpoint therapy by priming or sensitizing patients remains an area of active clinical and pre-clinical investigation across a variety of tumor types. The early clinical data for the value of an epigenetic priming paradigm (combination epigenetic therapy followed by immune checkpoint inhibition monotherapy), and which guided the initial design of this trial for advanced NSCLC, suggested priming could be operative – and it may be. However, for those patients with advanced NSCLC treated on the original epigenetic priming arm of this study, it is clear that any long priming phase will not be clinically tolerated by the majority of patients with advanced NSCLC because of the aggressiveness of the disease, and dictates a need to move the epigenetic therapy concurrent with immune checkpoint therapy. We have found success in treating aggressive malignant mouse models concurrently with epigenetic therapy and checkpoint inhibitors at the initiation of therapy.

Pre-clinical data from the Baylin and Zahnow laboratories at JHH, summarized below, shows that this is a potentially relevant area of clinical therapy across multiple tumor types and is an area of ongoing active investigation. To date, numerous mouse models in their laboratories have been treated with concurrent Azacitidine and checkpoint inhibitors without significant adverse events being noted. On the contrary, overall survival was optimized when using combination therapy consisting of epigenetic agents and immune checkpoint inhibitors.

Data in a mouse B6 melanoma model treated with Azacitidine and anti-CTLA-4 at the initiation of therapy[18] is presented in **Figure 1**. Significant anti-tumor effects were seen only with the combination of AZA and anti-CTLA-4 when compared to each drug alone. This difference was also seen in multiple decreasing doses of AZA in the combination treatment arm.

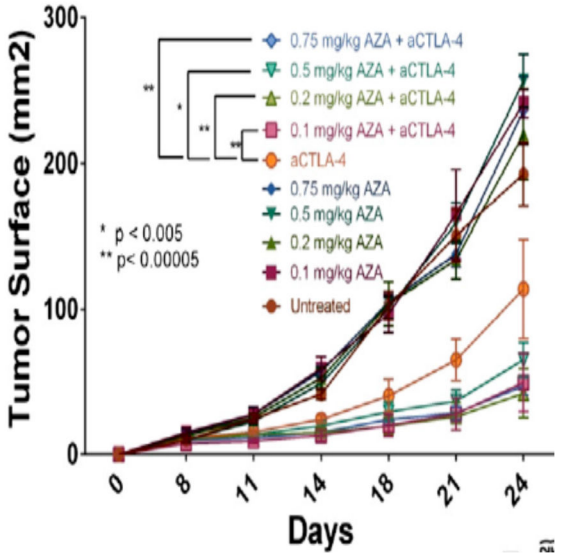


Fig. 1 Tumor responses of mice injected with B16-F10 cells and treated with either PBS, anti-CTLA-4, Aza, or both anti-CTLA-4 and Aza. *Data represent results from one of two independent experiments with identical results, each with n = 10 per arm. Y axis = mean tumor surface, error bars ± SEM. C57BL/6J mice were subcutaneously injected with 1 3 105 B16-F10 tumor cells. On days 4, 8, 11, 14, and 18, mice were treated intraperitoneally with 100 mg anti-ctla-4. Mice received two cycles of intraperitoneal injection of 0.1 to 0.75 mg/kg Aza in PBS for 5 consecutive days followed by 7 days off treatment, starting at day 8 after developing palpable tumors, with control groups receiving corresponding doses of non-specific isotype antibody control and PBS intraperitoneally.*

The Baylin lab has treated mouse models of NSCLC with a regimen of low dose Azacitidine + low dose HDAC inhibitor (ITF) and anti-PD1 (**Figure 2A**)[20]. The anti-PD-1 agent was administered at the end of the first 2 week first cycle with the first two drugs, and this cycle was repeated every two weeks for three months. The mice showed no toxicity and efficacy with respect to tumor reduction at 3 months is shown in **Figure 2B**.

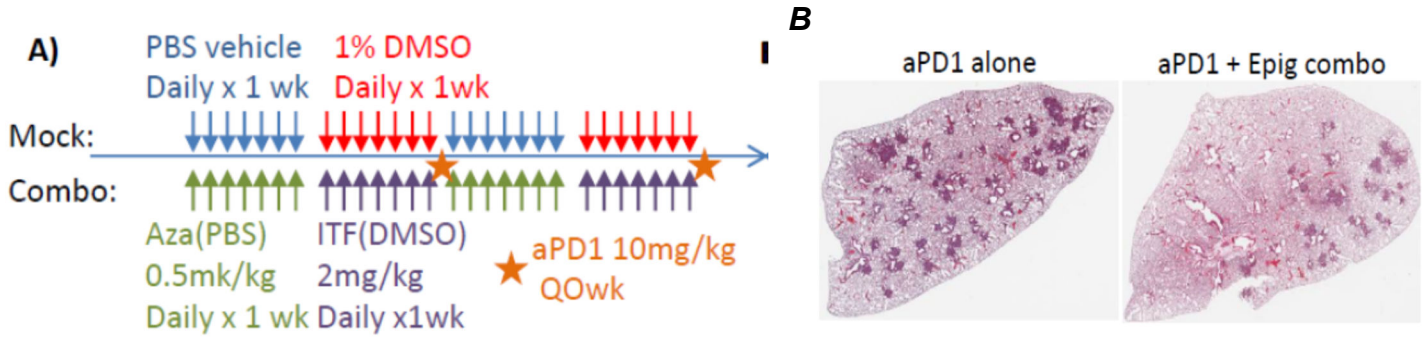


Fig. 2 Mock and combination regimen therapy in a mouse model of NSCLC. *A. Schema for dosing mock and combo regimens. B. In-vivo NSCLC mouse response to anti-PD1 alone versus anti-PD1 + Epigenetic combination therapy.*

The Zahnow lab has also treated a mouse model of serous ovarian carcinoma with this novel therapeutic combination[21]. In this therapeutic paradigm epigenetic agents were given in the first 2 weeks, and anti-PD1 was given concurrently with the epigenetic therapy for 2 weeks thereafter. The animals did not manifest toxicity and the efficacy is seen in the mouse survival curves (**Figure 3**) wherein the triplet therapy was most efficacious versus each agent alone or the combination of epigenetic drugs alone without anti-PD1.

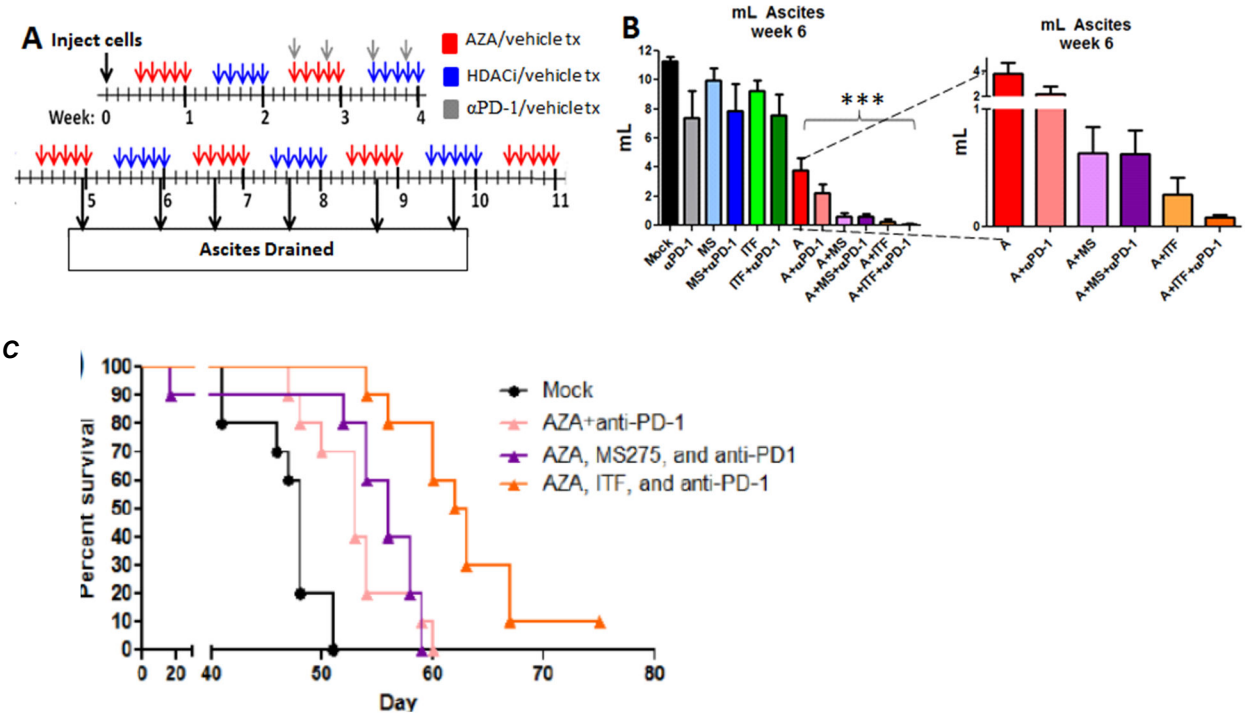


Figure 3: Combining epigenetic therapy and immunotherapy in an intact mouse model of ovarian cancer decreases tumor burden and increases survival. *2.5x105 cells were injected i.p. into 8-10 week old female C57/Bl6 mice. 3 days after injection, 0.5mg/kg AZA or saline was given i.p., for 5 days a week. The following week, 2mg/kg ITF2357 or MS275 or 1% DMSO in saline was injected i.p. for 5 days. For the rest of the experiment, the treatment alternated between AZA and HDACi every other week. Anti-PD-1 (200ug/mouse) was given on days 17, 20, 24, and 27 after injection. Tumor burden was measured by the weight gain and amount of ascites drained from the mice. A) Treatment schematic. B) mL of ascites fluid drained at week 6. C) Survival of the mice.*

This preclinical data consistently demonstrates across numerous animal models that tumor burden is decreased, overall survival is increased, and minimal toxicity is observed in mice receiving epigenetic therapy concurrent with checkpoint inhibitors. By giving the anti-PD-1 up front with epigenetic therapy, this novel combinatorial approach may be able to slow rapid tumor progression and thus give the epigenetic therapy more time to effectively increase TILs and sensitize the tumor microenvironment to immune checkpoint inhibition. This concurrent treatment paradigm also affords the ability to expose the tumor to epigenetic therapy for a longer period of time, thus maximizing it's potential effects as well.

2.5 Rationale for combining epigenetic therapy with immunotherapy following progression on anti-PD-1

2.5.1 Clinical Rationale for combination epigenetic and immunotherapy in PD-1 refractory or resistant disease

This amendment addresses the increasing complexity of standard of care NSCLC treatment with immunotherapy. The anti-PD-1 agent, pembrolizumab, is now approved

for the first line setting as monotherapy in advanced or metastatic PD-L1 positive (tumor proportion score (TPS)≥50%) NSCLC[24]. Also, due to recent results of KEYNOTE189, as well as previous results of KEYNOTE021 cohort G, the combination of pembrolizumab with carboplatin and pemetrexed chemotherapies is now considered standard of care for first line treatment of advanced or metastatic non-squamous NSCLC patients with good performance status, regardless of PD-L1 status[25,26]. While the response rates and overall survival are significantly better than chemotherapy alone, the majority of patients will either not respond or eventually develop PD-1 resistance. Therefore, further evaluation for therapeutic options that will reignite the ability for PD-1 to initiate a robust anti-tumor immune response are needed. This is especially true in KRAS mutated NSCLC, as many have co-inactivated tumor suppressor STK11/LKB1 genes, which have been shown to generate a proinflammatory, T-cell suppressive tumor microenvironment[27].

Recent data was released from Syndax regarding the ENCORE 601 trial, whose NSCLC patient cohort that enrolled patients with disease progression on or after anti-PD1/L1 therapy. The company reported that they had met their pre-specified objective response threshold to advance into the second stage of the Phase 2 trial[28]. This trial evaluates the combination of entinostat plus pembrolizumab in two NSCLC patient cohorts: those who had previously progressed on PD1/L1 therapy, and those patients that are anti-PD-1/L1 naïve.

Although trial data is not yet published, Mirati's class I HDACi mocetinostat has been combined with the anti-PD-L1 agent durvalumab in NSCLC, after it was shown to induce PD-L1 expression, improve tumor antigen presentation and facilitate efficient anti-tumor immune response by altering cellular subsets[29].

There is currently another trial in progress using guadecitabine (DNMTi) with durvalumab (anti-PD-L1) in advanced renal cell carcinoma, in both the immunotherapy naive and resistant patient populations. This is based on preclinical data showing that hypermethylation of CXCL9/10, important tumor microenvironment chemoattractants for activated Th1 and NK cells, is a significant immune evasion mechanism used in these tumors[30].

2.5.2 Pre-Clinical Rationale for combination epigenetic and immunotherapy in PD-1 refractory or resistant disease

The application of epigenetic therapy to PD-1 refractory or resistant disease represents an emerging area of inquiry with some preclinical data indicating efficacy. A recent publication by Youngblood and colleagues suggests that CD8 tumor infiltrating lymphocytes can become PD-1 refractory in the presence of continuous antigen exposure through the development of a fully exhausted population[31]. Therapeutic intervention with a demethylating agent prevented the emergence of this fully exhausted CD8 T cell population and thus enabled response to PD-1 in the Tramp-C2 murine model, which is endogenously refractory to immunotherapy. Additionally, a study by Baylin and colleagues demonstrated that combination epigenetic therapy (DNMTi+HDACi) can alter the CD8 T cell transcriptome, skewing from an exhausted to an effector/memory like population in a Kras driven murine NSCLC model[20]. These

studies suggest that epigenetic therapy can both modulate the T cell exhausted state and drive responses to immunotherapy in the setting of PD-1 refractory disease.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically proven stage IIIB, IV or recurrent non-small cell lung cancer. Patients must be willing to undergo a pre-treatment tumor biopsy, either core needle biopsy or equivalent amount or via excisional specimen (cytology specimen not acceptable for this purpose).

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. A CT scan of the abdomen and pelvis is not required for patients with no disease in these areas.

3.1.3 Age ≥18 years.
Because no dosing or adverse event data are currently available on the use of azacitidine with entinostat, or of Nivolumab, in patients <18 years of age, children are excluded from this study.

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.

3.1.5 Life expectancy of greater than 12 weeks.

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥2,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) ≤3 X institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance ≥40 mL/min for patients with creatinine levels above institutional normal.
- Resting and walking O2 saturation must remain above 90% at the time of screening

3.1.7 The effects of entinostat, azacitidine, and Nivolumab, on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for up to 23 weeks after the last dose of nivolumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men who are sexually active with

women of childbearing potential must also use an adequate contraceptive method for up to 31 weeks after the last dose of nivolumab.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 All adenocarcinoma patients must be tested for ALK rearrangements and EGFR (Exon 19 Deletion and Exon 21 L8585R Substitution) mutations and must have been treated with EGFR or ALK TKI therapy if found to have an actionable alteration. If patients are KRAS positive, testing for ALK rearrangements and EGFR mutations is not applicable.

3.1.10 All patients should have been offered a platinum-based chemotherapy. For EGFR/ALK wild type patients, no more than two prior chemotherapy-based lines of therapy for advanced or metastatic NSCLC is permitted. For EGFR mutated or ALK translocated patients, no more than three prior lines of therapy for advanced or metastatic NSCLC is permitted. Patients who refuse platinum based chemotherapy, may be allowed to enroll if they meet all other criteria.

3.1.10.1 Patients who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible and the adjuvant or neoadjuvant chemotherapy will count as a line of therapy as above.

3.1.10.2 Subjects with recurrent disease > 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen given to treat the recurrences, are eligible and do not count as another line of therapy for advanced disease.

3.1.10.3 Subjects who received pemetrexed, bevacizumab, or erlotinib as maintenance therapy (nonprogressors with platinum-based doublet chemotherapy) and subsequently progressed after maintenance therapy, are eligible and do not count as a line of therapy. However, subject who received a tyrosine kinase inhibitor after failure of a prior platinum-based therapy, that tyrosine kinase inhibitor therapy would count as an additional line of therapy.

3.1.10.4 Patients who have been treated with prior standard of care PD-1/L1 agents, alone or in combination with chemotherapy, are eligible. Patients previously treated on clinical trials with non PD-1/PD-L1 immunotherapy agents are eligible. Patients who have been treated with a PD-1/L1 agent in more than 1 line of therapy (as standard of care or in clinical trial) are **not** eligible.

3.1.11 Arm-specific eligibility criteria

3.1.11.1 Arm D: Anti-PD-1/PD-L1 treatment naïve patients only

3.1.11.2 Arm E & F: Anti-PD-1/PD-L1 treatment experienced patients: Patients must have had refractory (Arm E=less than 24 weeks from first dose of anti-PD-

1/PD-L1) or recurrent (Arm F=more than 24 weeks from first dose of anti-PD-1/PD-L1) disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy.

3.1.13 Patients must have disease amenable to biopsy at the time of enrollment as biopsies are required for study participation (see Study Calendar **Section 8**, for biopsy schedule by Arm).

3.2 Exclusion Criteria

3.2.1 Any active history of a known autoimmune disease. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.2 Subjects with a history of interstitial lung disease or lung disease that has required intubation in the past (i.e. such as Asthma or COPD)..

3.2.3 Patients who have had chemotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.

3.2.4 Patients who have had radiation therapy within 1 week prior to entering the study.

3.2.5 Patients who are receiving any other anticancer therapy.

3.2.6 Patients with uncontrolled brain metastases. Patients with brain metastases must have stable neurologic status following local therapy (surgery or radiation) for at least 2 weeks without the use of steroids or on stable or decreasing dose of $\leq$ 10mg daily prednisone (or equivalent), and must be without neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients with a history of carcinomatous meningitis are not eligible.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to entinostat, azacitidine, or Nivolumab.

3.2.8 Known or suspected hypersensitivity to azacitidine or mannitol

3.2.9 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, myocardial infarction or new onset angina within six months of enrollment, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Pregnant women are excluded from this study because entinostat, azacitidine, and Nivolumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants

secondary to treatment of the mother with entinostat, azacitidine, or Nivolumab breastfeeding should be discontinued if the mother is treated on this protocol.

3.2.11 HIV-positive patients are excluded. (Patients cannot have known history of HIV. Testing for it at baseline is not required unless it is suspected they may have it).

3.2.12 Patients with active hepatitis B or hepatitis C are excluded. (Patients cannot have known history of hepatitis B or hepatitis C. Testing for it at baseline is not required unless it is suspected they may have it).

3.2.13 Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids and adrenal replacement steroid doses $\leq$ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.2.14 Patients with malabsorption in the small intestine or other conditions that would preclude administration of oral medication.

3.2.15 Prior therapy with DNA methyltransferase therapy or HDAC inhibitor therapy.

Patients must meet all inclusion criteria and none of the exclusion criteria. Eligibility Waivers will not be granted.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Agent Administration

Patients will be treated by Arm according to disease status. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen description						
Agents	Premedications/instructions	Dose	Route	calendar	Cycle length	# of Cycles
Epigenetic component						
Arm D-F Azacitidine	5HT3 inhibitor PO or IV 30 min prior; rotate site of injection	40 mg/m^2	SC	Days 1-5, 8-10	28 days	6 Cycles
Arm D-F Entinostat	5HT3 inhibitor PO or IV 30 min prior; on an empty stomach	5 mg	PO	Days 3 and 10		

Immunotherapy component						
Arm C-F Nivolumab	Optional: acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV 30 min prior.	240 mg 480 mg (after Cycle 6)	IV	Days 1, 15 Day 1	28 days 28 days	Until PD^

^Patients are allowed to remain on nivolumab monotherapy treatment after the first documented PD if clinically stable. (See Section 4.4.1)

^After a patient has completed 6 months of nivolumab (regardless of arm assignment), they can receive nivolumab every 4 weeks instead of every 2 weeks.

4.1.1 Entinostat

Entinostat is an oral agent. Entinostat should be taken on an empty stomach (fasting) either at least 1 hour prior to a meal or at least 2 hours after a meal. The tablets should be taken one at a time. The tablets should not be split, crushed or chewed. Entinostat is known to cause nausea and vomiting. To reduce the incidence of nausea and vomiting associated with entinostat administration, patients will be instructed to take a 5-HT3 antagonist orally or IV 30-60 minutes prior to taking the dose of entinostat.

4.1.2 Azacitidine

Azacitidine is supplied as 100 mg of white, lyophilized powder with 100 mg of mannitol, USP in 30 ml flint vials. The contents of each vial should be dissolved in 4mL of sterile water or 0.9% sodium chloride to provide a 25 mg/ml slurry. Azacitidine does not go into solution but forms a loose slurry when reconstituted in this fashion. Reconstituted solutions of azacitidine are unstable. Upon reconstitution, the material should be injected within 60 minutes. The slurry should be injected subcutaneously. The slurry SHOULD NOT be injected intravenously. Doses may be split into multiple injection sites if volume to be administered is too large. Injection sites should be rotated on a daily basis.

4.1.3 Nivolumab

Nivolumab vials are to be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of BMS-936558 include laboratory coats and gloves. After Nivolumab been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. Stability data for Nivolumab following dilution and transfer to the IV bag supports either: 24 hours at 2°C to 8°C in the

refrigerator, or 4 hours at room temperature/under room light and 18 hours at 2°C to 8°C in the refrigerator. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between Nivolumab and polyolefin bags have been observed.

Nivolumab will be administered as an IV infusion as close to 30 minutes as possible, using a volumetric pump with a 0.2 micron in-line filter, followed by a saline flush. Nivolumab will be administered as a flat 240 mg dose or 480 mg every 4 weeks once the completion of cycle 6 has occurred. There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for Nivolumab on the first cycle. If an allergic reaction is noted, then acetaminophen 650 mg PO and diphenyhydramine 50 mg PO/IV may be administered prior to Nivolumab infusion.

4.2 General concomitant medication and supportive care guidelines

4.2.1 No investigational or commercial agents or therapies other than those described above may be administered with the intent to treat the malignancy.

4.2.2 Contraceptive therapy: Sexually active men and women of child-bearing potential must agree to use effective contraception.

4.2.3 Concomitant use of valproic acid is prohibited due to its known activity as a histone deacetylase inhibitor.

4.2.4 Nausea and vomiting after entinostat administration are expected. Prophylactic 5-HT3 inhibitors will be administered at least 30 minutes prior to ingestion of entinostat as well as on an as needed basis. Delayed nausea and vomiting is associated with azacitidine 4-6 hours after treatment. Prophylactic 5HT3 inhibitor will be administered 30 minutes prior to injection of azacitidine on days 1-5, and 8-10. Prochlorperazine and/or 5HT3 inhibitor may also be taken for delayed nausea as needed.

4.2.5 Diarrhea: **If diarrhea occurs during Nivolumab treatment, workup and treatment should follow the Nivolumab diarrhea toxicity treatment algorithm located in the appendix of the Nivolumab investigators brochure.**

4.2.6 Neutropenia without fever: The clinical situation should be closely followed for fever, focal signs of infection, and neutrophil nadir.

4.2.7 Neutropenia with fever: Hospitalization and urgent broad-spectrum antibiotics are required for this potentially life-threatening complication. The occurrence of a temperature higher than 38.3°C (100.9°F) demands prompt evaluation of blood counts and examination for source of infection.

4.2.8 Anemia: Red blood cell support should be given for any patient with symptomatic

anemia and is recommended for patients with asymptomatic anemia when hemoglobin is below 8 g/dL. Erythropoietin or darbepoietin may be used at the discretion of the investigator.

4.2.9 Thrombocytopenia: Platelet transfusion should be given for a platelet count below 10,000/mm3 in the absence of bleeding. If bleeding develops or invasive procedures are planned, platelet transfusion should be administered in accordance with standard practice.

4.2.10 Constipation: Constipation has been a common side effect of azacitidine and entinostat. Treatment with stool softeners and laxatives should be initiated early on to prevent symptoms from constipation.

4.2.11 The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event): immunosuppressive agents, immunosuppressive doses of systemic corticosteroids (except as noted in inclusion/exclusion section), Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (eg prednisone $\leq$ 10 mg/day) are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Sensitive substrates of CYP1A2, CYP2C8, CYP3A with a narrow therapeutic window are prohibited (including: Theophylline, tizanidine, paclitaxel, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus and terfenadine). Drugs that are known to inhibit or induce P-gp are prohibited (including: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, felodipine, lopinavir, quercetin, ranolazine, ticagrelor, ritonavir, cyclosporine, verapamil, erthyromycin, ketoconazole, itraconazole, quinidine, avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort, and tipranavir/ritonavir)

4.2.12 Non-palliative radiation therapy is not allowed. Palliative radiation therapy is only allowed during Nivolumab monotherapy, not during concurrent epigenetic therapy, if deemed necessary for the patient by the investigator. Palliative radiation therapy to the lung is not recommended.

If palliative radiotherapy is required, and the patient is currently receiving concurrent epigenetic therapy, the epigenetic therapy must be held. Upon completion of the palliative XRT, the patient may be allowed to resume study treatment with epigenetic therapy and nivolumab following the 1 week washout period.

If the patient is on single agent Nivolumab therapy when they require palliative radiation therapy, then Nivolumab should be withheld for at least 1 week before, during and 1 week after radiation. Patients should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to grade $\leq$ 1 prior to resuming Nivolumab.

4.3 Management of Nivolumab-related infusion reactions

Since Nivolumab contains only human immunoglobulin protein sequences, it has a low incidence of infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions must be reported as an SAE if it meets the criteria. Infusion reactions must be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below:

<u>For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated).</u>

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional Nivolumab administrations.

<u>For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours).</u>

- Stop the Nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before Nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

<u>For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated).</u>

- 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 1:1000 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 must be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators must follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.4 Duration of Therapy

Arm D: Epigenetic therapy (azacitidine and entinostat) in combination with nivolumab will be given for six 28-day cycles on this protocol. Patients experiencing adverse event(s) that in the view of the treating physician or principal investigator make six cycles undesirable, may continue with Nivolumab as a single agent after only 2 cycles of concurrent epigenetic therapy with Nivolumab. Please see section 4.4.1 regarding treatment at time of progressive disease (PD).

Arm E and Arm F: Epigenetic therapy (azacitidine and entinostat) in combination with nivolumab will be given for six 28-day cycles on this protocol. Patients experiencing adverse event(s) that in the view of the treating physician or principal investigator make six cycles undesirable, may continue with Nivolumab as a single agent after only 2 cycles of concurrent epigenetic therapy with Nivolumab. Please see section 4.4.1 regarding treatment at time of progressive disease (PD).

Nivolumab monotherapy on all Arms may continue until one of the following criteria applies and at that time, nivolumab treatment will be permanently discontinued:

- Any Grade $\geq$ 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related bronchospasm, hypersensitivity reactions, and infusion reaction:
  - Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following

criteria require discontinuation:

- AST or ALT > 5-10x ULN for > 2 weeks
- AST or ALT > 10x ULN
- Total bilirubin > 5x ULN
- Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:

  - Grade 4 neutropenia $\leq$ 7 days
  - Grade 4 lymphopenia or leucopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed after discussion with study PI.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

- Confirmed disease progression at time points after first cycle of nivolumab monotherapy. This allows for patients to remain on treatment with nivolumab after disease progression if clinically stable. However, once the next disease assessment confirms progression or if clinically unstable, patients must stop treatment. (See section 4.4.1)

- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s), not able to be managed by steroid/or other immunosuppressive therapy (such as infliximab or IVIG) administration.

- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.4.1 Treatment Beyond Disease Progression

Treatment beyond disease progression is allowed for patients receiving concurrent azacitidine, entinostat and nivolumab on Arm D, Arm E and Arm F. If disease progression (PD) is noted during the 6 cycles of concurrent therapy per RECIST 1.1, the patient may continue study treatment until disease progression is confirmed. If at that time disease progression (PD) is confirmed, the patient will come off study treatment. After 6 concurrent cycles, patients will continue nivolumab monotherapy treatment irrespective of disease

progression status, and will follow the decision to treat beyond disease progression (PD) as per below. If the noted PD requires palliative radiation therapy, please see Section 4.2.12 regarding subsequent study treatment.

Subjects being currently treated with nivolumab monotherapy on any study Arm will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of the study drug
4. Stable performance status
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastasis)

The decision to continue treatment beyond initial progression must be documented in the study records.

A radiographic assessment/scan will be performed at the end of the cycle following the original PD to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the patient receiving nivolumab monotherapy continues to achieve clinical benefit by continuing treatment, the subject may remain on the trial and continue to receive monitoring according to the Study calendar.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

For subject in either treatment arm, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as symptomatic deterioration. Every effort should be made to document objective progression (i.e. radiographic confirmation) even after discontinuation of treatment.

4.5 Duration of Follow Up

Once treatment has been discontinued, patients will be followed with phone calls every 3 months until death or for 5 years, whichever occurs first. We will collect data on development of additional cancers, subsequent therapy (chemotherapy, radiation or surgery) for their cancer, and survival. Medical records including laboratory, pathology, operative, and radiology reports will be obtained at the discretion of the principal investigator with permission from the

patient. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.6 Criteria for Removal from Study Treatment

A patient will be withdrawn from the study treatment if any of the following events occur while on therapy:

- Interruption of scheduled therapy for greater than 6 weeks except as noted above in section 4.4.
- Intolerable adverse effects, laboratory abnormality or intercurrent illness that is judged by the investigator to be either physically or psychologically detrimental to the patient.
- Pregnancy.
- Patient non-compliance.
- Unresolved or recurrent Grade 3 or 4 toxicities except as noted above in section 4.4.
- Treatment with other anti-cancer drugs.
- Confirmed disease progression on therapy as outlined in Section 4.4 and Section 4.4.1.
- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- All subjects who discontinue study treatment should comply with protocol specified follow-up and survival procedures as outlined in Section 4.5. The ONLY exception to this requirement is when a **subject withdraws consent** for all study procedures **or loses the ability to consent freely** (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness); in this case they will be deemed off study and no further follow up will be performed.

5. DOSING DELAYS/DOSE MODIFICATIONS

Dosing delays and dose modifications on this study will be made at the discretion of the treating physician. No dose modifications will be allowed for nivolumab. Adverse symptoms prompting dose delay of greater than 6 weeks in any phase of the study will result in study discontinuation except as noted in section 4.4.

5.1 Dose Modifications/Treatment Delays for Azacitidine and Entinostat Only

In order to maintain dose –intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified below. In case of toxicity, appropriate medical treatment should be used (including anti-emetics for nausea/vomiting, etc.) No dose escalation is planned for this study. For any event which is apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. (e.g. if a patient has a grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes). Where several toxicities with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.

Treatment will be modified based on treatment-related toxicity as described below for all patients receiving azacitidine and entinostat on Arm D, Arm E and Arm F. Dose omits due

to toxicity will not be made-up; patients may resume treatment once toxicity resolves as per the regular schedule.

5.1.1 White blood cell decreased/Neutrophil count decreased.

- See Table for dose adjustment criteria.
- Filgrastim or pegfilgrastim should not be given during nivolumab treatment.

5.1.2 Platelet Count Decreased.

- See table for the dose adjustment criteria.

5.1.3 Anemia

- There are no specific recommendations regarding management of anemia.
- Blood transfusions or erythropoietin stimulating agents may be used to treat chemotherapy-induced anemia at the discretion of the treating physician per current ASCO Guidelines. These state that “for patients with chemotherapy-associated anemia, initiating an erythropoiesis-stimulating agent (ESA) as hemoglobin (Hb) approaches, or falls below, 10 g/dL, to increase Hb and decrease transfusions”.

5.1.4 Diarrhea

If diarrhea develops, patient must be evaluated for potential signs or symptoms of infectious causes or nivolumab-related colitis. If these etiologies are excluded, patients will be instructed to begin taking loperamide at the earliest signs of:

- A loose stool.
- Occurrence of 1 to 2 more bowel movements than usual in one day, or Unusually high volume of stool,
- Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours (4mg every 4 hours while asleep) around the clock until diarrhea-free for at least 12 hours. Additional antidiarrheal measures may be used at the discretion of the treating physician.
- If the measures above fail, the dose may be reduced as listed below.

5.1.5 Nausea/Vomiting

- Both entinostat and azacitidine use can lead to nausea and vomiting.
- Prophylactic 5-HT3 antagonist will be used on days when either entinostat orazacitidine will be administered.If nausea and vomiting persists despite these measures, more aggressive use of5-HT3 antagonists or other anti-emetics can be used at the discretion of the treating physician.
    - See table below for the dose adjustment criteria.

5.1.6 Metabolic/electrolyte abnormalities

- Entinostat is associated with multiple electrolyte abnormalities including hypermagnesemia, hyperglycemia, hypophosphatemia, hyponatremia, and hypocalcemia. Low values will be repeated as appropriate per institutional standard. Hyperglycemia will be corrected at the discretion of the treating physician.
- See table for the dose adjustment criteria.

5.1.7 Other non-hematologic toxicities

- Dose adjustments will not be made for alopecia, fatigue, or loss of appetite of any grade.
- For other grade 3 and 4 non-hematologic toxicities not described above, see Table for dose adjustment criteria.

CTCAE System Organ Class (SOC)	**Adverse Event**	**Grade**	**Azacitidine Dose Change**	**Entinostat Dose Change**
Investigations	Neutrophil Count decreased	Grade 1 or 2	No Change	No Change
		Grade 3 or 4	Omit for 2 weeks and reduce next cycle by 10 mg/m^2	Omit for 2 weeks and reduce next cycle to 3 mg
	Platelet count decreased	Grade 1 or 2	No change	No change
		Grade 3 or 4	Omit for 2 weeks and reduce next cycle by 10 mg/m^2	Omit for 2 weeks and reduce next cycle to 3 mg
	White blood cell decreased	Grade 1 or 2	No change	No change
		Grade 3 or 4	Omit for 2 weeks and reduce next cycle by 10 mg/m^2	Omit for 2 weeks and reduce next cycle to 3 mg
Gastrointestinal disorders	Diarrhea (Reduce dose only after optimal use of loperamide**)**	Grade 1 or 2	No change	No change
		Grade 3 or 4	Omit for 2 Weeks and reduce next cycle by 10 mg/m^2	Omit for 2 weeks and reduce next cycle to 3 mg
	Nausea / Vomiting (reduce dose only after optimal use of	Grade 1 or 2	No change	No change

	anti-emetics)	Grade 3 or 4	Omit for 2 weeks and reduce next cycle by 10 mg/m^2	Omit for 2 weeks And reduce next cycle to 3 mg
Metabolism nutrition disorders	-Hyperglycemia -Hypoglycemia -Hypophosphatemia -Hyponatremia -Hypocalcemia -Hypercalcemia	Grade 1 or 2	No change	No Change
		Grade 3	No change	Omit for 2 weeks and reduce next Cycle to 3 mg if refractory to appropriate treatment
		Grade 4	No Change	Omit for 2 weeks and reduce next cycle to 3 mg
Other non-hematologic adverse events not mentioned above[2]		Grade 1 or 2	No change	No change
		Grade 3 or 4	Omit treatment until toxicity Resolves to Grade 1 then Dose reduce by 10mg/m^2	Omit treatment Until toxicity Resolves to Grade 1 then dose reduce to 3 mg

[1]If adverse events are noted on day 1 of any cycle of therapy then both agents should be held until treatment is deemed safe to administer. Unless otherwise specified, grade 3 or 4 toxicity should improve to grade 2 or better prior to resuming treatment.
[2]If treatment is omitted for non-hematologic adverse events not described above both drugs should be dose-reduced unless the toxicity can be clearly attributed to entinostat or azacitidine specifically.

5.1.8 Hypersensitivity Reactions

Hypersensitivity reactions to azacitidine or entinostat should be managed as per standard of care at the treating institution. Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Subjects who experience a severe hypersensitivity reaction to treatment should not be re-challenged.

5.1.9 Special Considerations

Up to 2 dose reductions are allowed for azacitidine and one dose reduction for entinostat. For any grade 4 toxicity that recurs despite prophylaxis or dose reduction, study treatment should be discontinued.

5.2 Nivolumab dose delay criteria

Nivolumab administration should be only delayed for the following immunologic toxicity:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leucopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leucopenia does not require dose delay.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.2.1 Criteria to Resume Treatment with Nivolumab

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (section 4.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to Baselin before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in section 4.4.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting in addition to routine reporting.

6.1 Adverse effects of azacitidine

Very common adverse effects of azacitidine (≥10%) include anemia which may require blood transfusion, febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, abdominal pain (including abdominal discomfort and upper abdominal pain), constipation, diarrhea, nausea, vomiting, asthenia, chest pain, fatigue, injection site erythema, injection site pain, injection site reaction, pyrexia, nasopharyngitis, pneumonia (including bacterial, fungal and viral), weight loss, decreased appetite, hypokalemia, arthralgia, musculoskeletal pain (includes back pain, bone pain and pain in extremity), myalgia, dizziness, headache, insomnia, dyspnea, epistaxis, ecchymosis, petechiae, pruritus (includes pruritus generalized) and rash.

Common adverse effects of azacitidine (≥1%-≤10%) include bone marrow failure, pancytopenia, conjunctival hemorrhage, eye hemorrhage, dyspepsia, gastrointestinal hemorrhage (includes mouth hemorrhage), gingival bleeding, hemorrhoidal bleeding, stomatitis, catheter site hemorrhage, chills, injection site bruising, injection site discoloration, injection site hematoma, injection site hemorrhage, injection site induration, injection site inflammation, injection site nodule, injection site pruritus, injection site rash, malaise, cellulitis, diverticulitis, neutropenic sepsis, oral fungal infection, pharyngitis, respiratory tract infection (including bronchitis and upper respiratory tract infection), rhinitis, sepsis (including bacterial, fungal and viral), sinusitis, skin infection, urinary tract infection, blood creatinine increased, dehydration, muscle spasms, intracranial hemorrhage, lethargy, somnolence, syncope, anxiety, hematuria, renal failure, shortness of breath on exertion (Dyspnea exertional), laryngeal pain, pleural effusion, alopecia, erythema, skin lesion, urticarial, hematoma, hypertension and orthostatic hypertension.

Uncommon adverse effects of azacitidine (≥0.1%- <1%) include hypersensitivity.

6.2 Adverse effects of entinostat

Common adverse effects of entinostat occurring in over 20% of patients, include anemia, diarrhea, nausea, vomiting, fatigue, anorexia, neutropenia, thrombocytopenia, hypoalbuminemia, hyponatremia, hypophosphatemia, leukopenia and headache.

Less common adverse effects include neutropenic fever, abdominal pain, constipation, pyrosis, peripheral edema, fever, chest pain, infection, hepatitis and liver dysfunction, renal insufficiency, lymphopenia, leucopenia, dehydration, hypocalcemia, hypokalemia, hypomagnesemia, myalgias, arthralgias, dysgeusia, cough, and dyspnea.

Rare but serious adverse effects have included erythema multiforme.

6.3 Adverse effects of Nivolumab

Very Common adverse effects of Nivolumab, occurring in ≥10% of patients, include fatigue, rash, diarrhea, and pruritus.

Common adverse effects (>1-9%) Include abdominal pain, alkaline phosphatase increased: lab test result associated with liver or bone abnormalities, allergic reaction/hypersensitivity, ALT increased: lab test result associated with abnormal liver function, Amylase increased: lab test result associated with pancreas inflammation, AST increased: lab test result associated with abnormal liver function, bilirubin (liver function blood test) increased, chills, constipation, cough, creatinine increased: lab test result associated with decreased kidney function, decreased appetite, dizziness or vertigo (feeling off balance which can lead to dizziness), dry mouth, dry skin, fever, headache, increased blood sugar, inflammation of the colon, inflammation of the mouth, infusion related reaction, lipase increased: lab test result associated with pancreas inflammation, loss of color (pigment) from areas of skin, lung inflammation (pneumonitis - see details below), musculoskeletal pain, nausea, redness (of the skin), shortness of breath, sodium levels in the blood low, swelling (including face, arms, and legs), thyroid gland function decreased, thyroid gland function increased, thyroid stimulating hormone increased (lab test associated with abnormal thyroid function), tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet, and vomiting.

Uncommon adverse effects (>0.1%-1%) include adrenal gland function decreased, bronchitis, dehydration, diabetes, double Vision, dry eye, erythema multiforme, hair loss, heart rate increased, heart rhythm abnormal, high blood pressure, hives, inflammation of the eye, inflammation of the kidney, inflammation of the pancreas, inflammation of the pituitary gland, inflammation of the stomach, inflammation of the thyroid gland, joint pain or stiffness, liver inflammation, low blood pressure, muscle inflammation, pemphigoid: blistering of the skin or mouth caused by the immune system attacking healthy tissue, pituitary gland function decreased, psoriasis: characterized by patches of abnormal, scaly skin, renal (kidney) failure or kidney injury, respiratory failure, upper respiratory tract infection, and vision blurred.

Rare, but serious adverse effects (≤1%) have included pneumonitis resulting in hypoxia and death, anaphylactic reaction (severe allergic reaction), cranial nerve disorder, damage to the protective covering of the nerves in the brain and spinal cord, diabetes complications resulting in excess blood acids, disease caused by the body's immune system attacking healthy organs, drug induced liver injury, Guillain-Barre syndrome (an autoimmune disorder associated with progressive muscle weakness or paralysis) inflammation of blood vessels, inflammation of the brain, potentially life-threatening or fatal, inflammation of the lining of the brain and spinal cord, inflammation of the heart, lung infiltrates (associated with infection or inflammation), Myasthenic syndrome (neurologic syndrome characterized by muscle weakness including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles) Polymyalgia rheumatic, Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys, Rosacea: acne-like skin condition resulting in redness of face, rupture of the intestine/hole in the intestine, Sarcoidosis (a disease involving abnormal collections of inflammatory cells (granulomas) in

organs such as lungs, skin, and lymph nodes), Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin, syndrome associated with fever, white blood cell activation and abnormal function (including destruction of other blood cells by certain white blood cells), low blood cell counts, rash, and enlargement of the spleen, toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis (disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains) and Vogt Koyangi Harada syndrome (a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision, the ear leading to hearing loss, ringing in the ears and/or the skin leading to loss of skin color), Fulminant type 1 diabetes mellitus, hepatic enzyme increased, immune-mediated nephritis and immune-mediated pneumonitis.

Of particular concern is pneumonitis, reported in approximately 3% of patients, including 3 fatalities.

6.4 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.5 Adverse Event Reporting

The principal investigator will notify the appropriate regulatory agencies of any serious adverse event due to any cause during the course of this investigation. These include the Johns Hopkins Cancer Center Data and Safety Monitoring Committee, and the Johns Hopkins Medical Institutional Review Board (JHM-IRB) of The Johns Hopkins Medical Institutions. The required reporting time period is 3 days for fatal events, and 10 days for all other events.

Adverse event information will be collected for the duration of the study. Patients will be instructed to notify investigators of any symptoms, and investigators will assess patients for adverse events at each visit. All toxicity and adverse events will be recorded on Case Report Forms, graded as to the severity and relationship to the study drug, and reported within the required time frame.

6.5.1 Adverse event reporting period

All SAEs, whether related or unrelated to nivolumab, azacitidine, and / or entinostat and all pregnancies must be reported to the Coordinating Center within 24 hours for reporting to BMS, Syndax, and Celgene (by the investigator or designee) within 24 hours of knowledge of the event.

For studies conducted under an **Investigator IND**, any event that is both **serious and unexpected** must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

Any investigational safety event that meets the requirements for 15-day reporting or follow-up reporting should not be sent via email, fax, or other rapid communication, but instead should be formally submitted to the IND directly, unless FDA has requested specific information on an event that requires rapid communication (such as an information request response).

SAEs should be reported on MedWatch Form 3500A or similar form. It MUST include the institutional **AND** BMSstudy ID [per study Agreement]

MedWatch SAE forms meeting the expedtided reporting requirments should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 301-796-9849 (DOP2 Fax number)
Meredith.libeg@FDA.HHS.Gov *(emails may be sent by the Study PI or an authorized party only)*
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
SAE Email Address: Worldwide.Safety@BMS.com

Expedited Reporting by Investigator to Celgene
Serious adverse events (SAE) are defined above. The Coordinating Center must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (VZ-CL-NSCLC-PI-003404) and the institutional

protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

The study period during which adverse events will be reported is from the initiation of study procedures to the end of the study treatment follow-up, defined as 100 days following the last administration of nivolumab treatment.

Expedited Reporting by Investigator to Syndax
Serious adverse events (SAE) are defined above. The Coordinating Center must inform Syndax in writing using a Syndax SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Syndax by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Syndax tracking number and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Syndax. A copy of the fax transmission confirmation of the SAE report to Syndax should be attached to the SAE and retained with the patient records.

Syndax Drug Safety Contact Information:
Syndax Pharmaceuticals, Inc.
Drug Safety and Regulatory
Attn: Miranda Rees
400 Totten Pond Road, Suite 110
Waltham, MA
Main: 781-419-1400
Direct: 781-419-1417
E-mail: aereporting@syndax.com; syndaxprogram@parexel.com; jnunes@syndax.com

The study period during which adverse events will be reported is from the initiation of study procedures to the end of the study treatment follow-up, defined as 100 days following the last administration of nivolumab treatment.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available,

a follow-up SAE report should be sent to BMS, Celgene, and Syndax using the same procedure used for transmitting the initial SAE report.

In accordance with local regulations, BMS, Celgene and Syndax will notify investigators of all SAEs that are suspected (related to their respective investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

6.5.2 Adverse event definition

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries are regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

6.5.3 Serious adverse event definition

A **serious adverse event** is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

6.5.4 Important medical event definition

Important medical events are those that may not be immediately life threatening, but are judged by the study investigator to be of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

6.6 Data Handling and Record Keeping

6.6.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

6.6.2 Source Documents

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

6.6.3 Case Report Forms

The study case report forms (CRFs) are the primary data collection instrument for the study. All data requested on the CRF will be recorded for each subject. If a procedure was not done or a question was not asked, this will be recorded as “N/D”. If the item is not applicable to the individual case, this will be recorded as “N/A”. CRFs will be built electronically in CRMS. All data will be entered electronically onto the electronic CRF through CRMS by the Study Coordinator and/ or Data Manager from each site. RedCap will be used for Data Analysis purposes by the Johns Hopkins Biostats team, but it will not contain CRFs.

6.6.4 Auditing and Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, University compliance and quality assurance groups and the Coordinating Center of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

6.6.5 Treatment Arm Assignment

There will be no randomization for treatment in Arm D, Arm E and Arm F. Arm assignment will be based on previous immune-oncology (IO) treatment status, as well as time from last IO treatment.

Arm D (naïve): previously treated recurrent or metastatic NSCLC, IO treatment naïve.
Arm E (refractory): previously treated recurrent or metastatic NSCLC, previous IO treatment with progression of disease within (≤) 24 weeks of first IO dose.

Arm F (resistant): previously treated recurrent or metastatic NSCLC, previously treated with IO therapy, with initial clinical benefit defined by disease progression seen after > 24 weeks since first dose of IO therapy.

6.7 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made to the investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Patients will also be required to reconsent for treatment beyond disease progression while on nivolumab.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this study can be found in Section 6.1.

7.1 Azacitidine

7.1.1 Chemical Name: 4-Amino-1-ß-D-ribofuranosyl-1,3,5-triazin-2(1H)-one
Other Names: 5-Azacitidine, 5-AZA, Mylosar7, Ladakamycin, Vidaza

7.1.2 Azacitidine will be supplied by Celgene Corporation. It will be supplied as 100 mg of white, lyophilized powder with 100 mg of mannitol, USP in 30 ml flint vials. The contents of each vial should be dissolved in 4mL of sterile water or 0.9% sodium chloride to provide a 25 mg/ml slurry. Azacitidine does not go into solution but forms a loose slurry when reconstituted in this fashion. Do not inject the slurry intravenously. Doses may be split into multiple injection sites if volume to be administered is too large. Injection sites should be rotated on a daily basis.

7.1.3 Storage and Stability: Store the intact vials at refrigeration temperature (2- 8 degree centigrade). The intact vials are stable for at least 4 years at refrigeration temperature. The constituted solutions hydrolyze at room temperature and should be used within 60 minutes for delivery of maximum potency.

7.1.4 Route of Administration: Subcutaneous injection. Patients will have their azacitidine injections administered in the outpatient clinic by a health care professional according to the standard chemotherapy administration protocol of the Cancer Center. Reconstituted solutions of azacitidine are unstable. Upon reconstitution, the material should be injected within 60 minutes.

7.1.5 Azacitidine will be supplied by Celgene Corporation. The IDS Pharmacy will be responsible for ordering study drug directly from Celgene Corporation.

7.2 Entinostat

7.2.1 Chemical name: 3-Pyridylmethyl N-{4-[(2-aminophenyl)carbamoyl]benzyl}carbamate

- Other names: MS-27-275, MS-275, SNDX-275
- Molecular Formula: C21H20N4O3 M.W.: 376.41
- Classification: Antineoplastic; entinostat is an inhibitor of histone deacetylase

7.2.2 How Supplied: entinostat is supplied by Syndax as a 1 mg (pink to light red, in bottles of 40), or 5 mg (yellow, in bottles of 40) film-coated tablets (round-biconvex). Each tablet also contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate. The film coating consists of hypromellose, talc, titanium dioxide and ferric oxide pgments (red and yellow) as colorants.

7.2.3 Mechanism of Action: entinostat is a histone deacetylases (HDACs) which is a family of enzymes that regulates chromating remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Entinostat inhibits histone deacetylases, changes chromatin configuration, and induces differentiation and apoptosis of cancer cells through an epigenetic mechanism. Among the genes whose expression is induced by entinostat is p21WAF-1/CIP-1, independent of p53 activity. The induction of p21, in turn, is thought to be responsible for the cell cycle arrest (at least in part through reduction of retinoblastoma protein phosphorylation) and antiproliferative activities of entinostat seen in multiple malignant cell types. In addition to its ability to bypass p53-dependent pathways, entinostat also appears to be independent of the presence and magnitude of multidrug resistance–1 (MDR) gene/protein expression.

7.2.4 Route of Administration: Oral. Entinostat should be taken fasting either at least 1 hour prior to or at least 2 hours after a meal. If the patient's dose requires more than one tablet, the tablets should be taken one at a time. Entinostat tablets should not be split, crushed or chewed.

7.2.5 Storage and Stability: Store the bottles at room temperature (15-25°C) and protect from light. Entinostat is not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC). Shelf life stability studies of the intact bottles are on-going.

7.2.6 Potential Drug Interactions: Studies examining interactions between entinostat and other agents have not been conducted.

7.2.7 Entinostat will be supplied by Syndax Pharmaceuticals Inc. The IDS Pharmacy will be responsible for ordering study drug directly from Syndax Pharmaceuticals Inc.

7.3 Nivolumab

7.3.1 Fully human anti-PD-1 IgG4:κ monoclonal antibody
Other names: BMS-936558, MDX-1106
Classification: Monoclonal antibody; impedes PD-1/PD-L1 interaction

7.3.2 How Supplied: Nivolumab is provided as a sterile liquid in vials each containing 100mg/10ml of the monoclonal antibody.

7.3.3 Mechanism of Action: Nivolumab is a monoclonal antibody that binds to the cell surface protein PD-1, a key regulator of cytotoxic T lymphocyte activation. Nivolumab inhibits PD-1/PD-L1 and PD-1/PD-L2 interaction, facilitating CTL reactivity and promoting an anticancer cytolytic response.

7.3.4 Route of Administration: Nivolumab is to be administered as an intravenous infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an intravenous push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline. A 30 minute infusion, can be diluted with 0.9% NS for delivery but the total drug concentration of the solution cannot be below 0.35mg/ml.

7.3.5 Storage and Stability: Nivolumab Injection: Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

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 (up to 25°C, 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

7.3.6 Potential Drug Interactions: Studies examining interactions between Nivolumab and other agents are ongoing.

7.3.7 Nivolumab will be supplied directly from BMS Inc.. The IDS Pharmacy will be responsible for ordering the study drug directly from BMS Inc.

7.3.8 Pharmacy: Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (eg, 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. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection or 5% dextrose injection to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kg of patient weight.

During drug product preparation and handling, vigorous mixing or shaking is to be

avoided. Instructions for dilution and infusion of nivolumab injection will be provided to the clinical site. Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, and glass bottles.

The placebo for nivolumab injection is administered in a similar manner as described above for the active drug product.

8. STUDY CALENDARS

Pre-study laboratory and exam evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Pre-study scans and x-rays must be done ≤4 weeks +/- 1 week prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. ***All time points on study have leeway of plus or minus 3 days unless otherwise noted.***

NOTE: *In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.*

ARM C: Nivolumab control arm (Will not continue enrollment)

	Pre-Study	28 day cycles (repeat)					
		Week 1	Week 2	Week 3	Week 4	Week 32	Follow up
Nivolumab [1]		X		X			
Informed Consent	X						
History & Physical[2]	X	X		X			
Concurrent Meds	X	X		X			
CBC and Chemistry[3]	X	X		X			
Research Bloods [4]	X	X[4]					
β-HCG	X						
AE assessment	X	X		X			
MRI or CT Scan of Brain	X						
CT or MRI for Tumor Assessment [5]	X[5*]				X[5*]	X[5*]	
Tumor Biopsy[6]	X						
Review of medical records, telephone							**Every 3 months up**

contact for recurrence-free and overall survival		**to 5 years**

1. 240 mg IV; After a subject has completed 6 months of nivolumab, they can receive nivolumab 480 mg every 4 weeks instead of every 2 weeks.
2. History and physical, includes interval history, oncologic driver mutation, smoking history, vital signs, oxygenation at rest and walking, height, weight, and performance status
3. Complete blood count and differential, and comprehensive metabolic panel, NOTE -TSH, Free T4 once every 28 days.
4. Plasma for assessment of methylation, peripheral blood lymphocytes for assessment of gene expression WILL BE COLLECTED PRIOR TO NIVOLUMAB ADMINISTRATION at baseline or day 1, week 5, week 9, week 17, week 25 and at progression (please see lab manual).
5. Tumor assessment includes radiologic assessment for RECISTv1.1 evaluation. Repeat radiologic assessment at week 8-9 and every 8 weeks thereafter while patient continues to receive Nivolumab. ***During week 24, whenever that falls, tumor radiologic assessment for RECISTv1.1 evaluation for the primary endpoint will occur no matter where that falls during the cycle or treatment with nivolumab.**
6. Tumor biopsy is required prior to INITIATION OF NIVOLUMAB, and at the time of progression. Biopsy at the time of progression should be conducted as soon as possible following imaging-confirmed disease progression.

Arm D, E and F: Epigenetic and Nivolumab Combination Therapy

	Pre-study	Cycle 1-6				Nivolumab monotherapy				
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	Follow up
Azacytidine [1]		d 1 - 5	d 8 - 10							
Entinostat [2]		d 3	d 10							
Nivolumab[10]		D1		D15		D1		D15[10]		
Informed Consent	X									
History & Physical [3]	X	X		X		X		X[10]		
Concurrent Meds	X	X	X			X	X			
CBC and Chemistry [4]	X	X	X	X		X		X[10]		
Research Bloods [5]	X	X[5]				X[5]				
β-HCG	X									
AE assessment	X	X	X	X		X		X[10]		
CT or MRI for Tumor Assessment[6]	X				X				X	
MRI or CT with contrast of Brain	X									
Tumor Biopsy	X[7]		X[8,9]	X[8]	X[9]				X[9]	
Review of medical records, telephone contact for recurrence-free and overall survival										**Every 3 months up to 5 years**

1. 40 mg/m2 s.c. days 1 – 5 and 8 – 10
2. 5 mg PO days 3 and 10
3. History and physical, includes interval history, oncologic driver mutation, smoking history, vital signs, oxygenation at rest and walking, height, weight, and performance status
4. Complete blood count and differential, comprehensive metabolic panel, serum magnesium and serum phosphate. Note-TSH, Free T4 once every 4 weeks.

5. Plasma for assessment of methylation, peripheral blood lymphocytes for assessment of gene expression WILL BE COLLECTED PRIOR TO TREATMENT ADMINISTRATION at baseline or day 1, week 5, week 9, week 17 and week 25 and at progression (please see lab manual).
6. Tumor assessment at all later time points include radiology scans to be performed every 8 weeks. The window is +/- 1 week.
7. Tumor biopsy required prior to treatment initiation.
8. Required on treatment biopsy should be performed during Cycle 2 Week 2 or 3 FOLLOWING completion of epigenetics for that cycle; must be completed prior to Cycle 3 dosing.
9. Required biopsy at time of disease progression while on combination therapy or nivolumab monotherapy per patient course. Biopsy at the time of progression should be conducted as soon as possible following imaging-confirmed disease progression.
10. After a subject has completed 6 months of nivolumab, they can receive nivolumab 480 mg every 4 weeks instead of every 2 weeks. Day 15 lab assessments, history and physical and AE assessments are not required for patients receiving nivolumab every 4 weeks. These assessments will be captured on day 1 of every cycle for subjects on Nivolumab every 4 weeks.

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

On this study, planned radiologic evaluations will be performed at baseline (within 4 weeks prior to starting study therapy) and then every 8 weeks. For all Arms, confirmatory scans should be obtained not less than 4 weeks following initial documentation of objective response, and will typically be obtained at the time of the next planned evaluation (i.e. 8 weeks following).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009], Changes in the longest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECISTv1.1 criteria. RECIST readers will be blinded to the treatment assignment of all subjects.

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since starting nivolumab treatment, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as per Section 4.4.1.

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on protocol.

Evaluable for objective response. Response to azacitidine/entinostat and to Nivolumab, will be assessed separately. For each, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first cycle of either therapy will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

9.1.2 Disease Parameters

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

Measurable disease. 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 or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

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.

Non-measurable disease. 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, lymphangitic involvement of the skin or lung, inflammatory breast disease, and abdominal masses/abdominal organomegaly (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 patient, these are preferred for selection as target lesions.

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.

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.

9.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT

scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECISTv1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST v1.1 measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate

cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments related to NSCLC management and to immunotherapy need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of tumor progression (particularly possible 'new' disease) or regression (evaluation of potential CR). Lesions can be assessed on FDG-PET imaging according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

9.1.4 Response Criteria

9.1.4.1 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.

Special notes on the assessment of target lesions:
Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm. When such a lesion becomes difficult to assign an exact measurement, it is recommended to: If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).
Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

9.1.4.2 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 patient 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 treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator). *When the patient also has measurable disease:* To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. *When the patients has only non-measurable disease:* To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

9.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

9.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

9.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

10.1.1 Study Design

The study is a non-randomized phase II study of nivolumab with concurrent epigenetic therapy (consisting of azacitidine and entinostat) for 6 cycles, followed by nivolumab monotherapy until confirmed disease progression is noted. We are evaluating the strategy of combination epigenetic therapy with Nivolumab in three distinct patient populations: PD-1/PD-L1 naïve, PD-1/PD-L1 refractory (previously treated with disease progression ≤ 6 months from first dose) and PD-1/PD-L1 resistant (previously treated with disease progression > 6 months from first dose). This study is intended to identify response to this regimen in the three patient groups.

10.1.1.1 Arms/Regimens

All patients on each of the three arms will receive the same treatment of epigenetic therapy. The treatment consists of azacitidine 40 mg/m2/day subcutaneously days 1-5 and 8-10 and entinostat 5 mg PO days 3 and 10 on a 28 day cycle concurrently with nivolumab for 6 cycles, followed by nivolumab until confirmed disease progression.

The arms are as follows:

Arm D: PD-1/PD-L1 naïve
Arm E: PD-1/PD-L1 refractory (i.e., previously treated with disease progression ≤ 24 weeks from first dose)
Arm F: PD-1/PD-L1 resistant (i.e., previously treated with disease progression > 24 weeks from first dose).

10.1.2 Endpoints

Primary Endpoint

Overall response rate (ORR)
Response, by Arm, will be measured per RECIST 1.1, as described in Section 9.

Secondary Endpoints

Progression free survival
Progression-free survival (overall) will be measured from the time of first dose of therapy until radiologic or clinical progression is noted or death from any cause.

Time to Progression
Time to progression will be measured from the time treatment begins until radiologic or clinical progression is noted.

Overall survival (OS)
Overall survival will be measured from the time of randomization until death from any cause.

Safety and tolerability
Toxicities observed in the study will be assessed by CTCAE 4.0 criteria. We will tabulate toxicities and compare the two treatment groups via methods appropriate for categorical data.

Feasibility
Feasibility for the purposes of this study means the ability for a patient to take the full course of their assigned treatment (minimum of six cycles) through 24 weeks, except for progression or death.

Exploratory Endpoints

Laboratory correlates of response
See section 11. These analyses are considered exploratory.

10.2 Sample size, Analysis, and Accrual Rate

The study will enroll up to 20 patients on Arm D, 20 patients on Arm E and 20 patients on Arm F. With this amendment, there will be no further enrollment for treatment on Arm C, although these patients will be allowed to cross over to Arms E or F if they progress and are otherwise eligible. The sample size is driven by what we think is feasible for enrollment over a reasonable period of time (e.g., a few years). We are including futility analyses within each Arm to allow us to stop a treatment arm if it appears not to have enough activity to warrant further investigation. Additionally, we have interim analyses to assess the feasibility of continuing an arm, with feasibility defined in the previous subsection.

The final analysis for each arm will be descriptive, consisting of summary statistics and confidence intervals. We will use survival analysis methods (e.g., the Kaplan-Meier survival estimation) for time-to-event data. We will not adjust for multiple comparisons; the futility analyses do not inflate the type I error, as seen in the simulation results (see section 10.4). Allowing for up to 10% inevaluable patients, we will enroll up to 22 patients on each Arm, or a total of 66. Anticipated accrual rate is 5 patients per month.

10.3 Stratification Factors

There are no stratification factors in this study. Patients will be assigned treatment Arm based on prior therapeutic regimen and disease response to that regimen.

10.4 Interim Analyses

The study design calls for interim futility analysis by arm. These analyses will occur separately by arm once 10 patients are on an arm and have either received at least 6 cycles of therapy or experienced a PFS event. Subsequent analyses will occur after 15 patients have either received at least 6 cycles of therapy or experienced a PFS event. The final analysis will occur after 20 patients have entered and received full therapy (6 cycles). The futility analysis is based on Bayesian hypothesis testing[32].

For Arm D, we take the expected ORR to be 20% if epigenetic therapy does not increase the clinical effectiveness of nivolumab alone. This estimate is based on results of the Checkmate studies (CheckMate 057 (non-squamous NSCLC) ORR = 19%; CheckMate017 (squamous cell NSCLC) ORR = 20%). We would consider the addition of epigenetic therapy encouraging if the ORR is 35% or higher. The study will stop for futility if we see 0 responses among the first 10 patients or no more than 1 response in the first 15 patients. We will not consider this Arm promising if we see 3 or fewer responders out of 20 patients. The following table provides the operating characteristics for Arm D based on 5000 simulations.

Simulation Results for Arm D

Scenario	Assumed true response rate	Pr(Stop for inferiority)	Average # patients treated (10%, 25%, 50%, 75%, 90%)
1	0.1	0.876	15.4 (10, 10, 15, 20, 20)
2	0.15	0.662	17.3 (10, 15, 20, 20, 20)
3	0.2	0.434	18.51 (10, 20, 20, 20, 20)
4	0.25	0.243	19.25 (20, 20, 20, 20, 20)
5	0.3	0.119	19.61 (20, 20, 20, 20, 20)
6	0.35	0.047	19.86 (20, 20, 20, 20, 20)
7	0.4	0.021	19.92 (20, 20, 20, 20, 20)
8	0.45	0.008	19.96 (20, 20, 20, 20, 20)
9	0.5	0.002	19.99 (20, 20, 20, 20, 20)

For Arms E and F, respectively, we take the expected ORR to be virtually 0% if epigenetic therapy does not increase the clinical effectiveness of nivolumab alone. We would consider the addition of epigenetic therapy encouraging if the ORR is at least 10%. The study will stop for futility if we see 0 responses among the first 15 patients. We will not consider an

Arm promising if none of the 20 patients on that Arm responds. The following table provides the operating characteristics for Arms E and F, respectively, based on 5000 simulations.

Simulation Results for Arm E and for Arm F

Scenario	Assumed true response rate	Pr(Stop for inferiority)	Average # patients treated (10%, 25%, 50%, 75%, 90%)
1	0.025	0.683	16.58 (15, 15, 15, 20, 20)
2	0.05	0.462	17.69 (15, 15, 20, 20, 20)
3	0.1	0.206	18.97 (15, 20, 20, 20, 20)
4	0.15	0.085	19.58 (20, 20, 20, 20, 20)
5	0.2	0.037	19.82 (20, 20, 20, 20, 20)
6	0.25	0.013	19.93 (20, 20, 20, 20, 20)
7	0.3	0.006	19.97 (20, 20, 20, 20, 20)
8	0.35	0.002	19.99 (20, 20, 20, 20, 20)
9	0.4	0	20 (20, 20, 20, 20, 20)

10.5 Feasibility monitoring

We will use separate Bayesian calculations to monitor the feasibility of each treatment. We define feasibility as the ability for a patient to take their full course of their assigned treatment (minimum of six cycles) through 24 weeks, except for progression or death. If there is considerable probability (≥ 67%) that the regimen is feasible for less than half of the patients, we will consider stopping the study. We will base the decision on the posterior probability that the treatment is not feasible (> 50% of patients who do not progress or die before 24 weeks do not make it to 24 weeks). The prior distribution for this calculation is Uniform (0,1). We will apply the monitoring rule separately by treatment group, and the analysis will occur at the time of each interim analysis. For each treatment Arm, though, we will apply the rules to all patients pooled together, rather than separately within each subtype, since we do not expect one group to be at greater risk of toxicity than the other. We will consider stopping the study if the data indicate that the treatment regimen is feasible for less than half of all patients, where we quantify certainty as two thirds or greater (i.e., 2:1 odds it is not feasible).

Rule: Stop if there is two-thirds (2:1 odds) or greater probability that 50% or more patients cannot complete at least 6 cycles of therapy (24 weeks), unless the patient's disease progressed or the patient died. The following table shows the stopping boundaries for monitoring that starts at the fifth patient.

Stop if not feasible for	Probability that feasibility > 50% =
4 out of 5 patients.	0.891
4 out of 6 patients.	0.773
5 out of 7 patients.	0.855
5 out of 8 patients.	0.746
6 out of 9 patients.	0.828
6 out of 10 patients.	0.726
7 out of 11 patients.	0.806
7 out of 12 patients.	0.709
8 out of 13 patients.	0.788
8 out of 14 patients.	0.696
9 out of 15 patients.	0.773
9 out of 16 patients.	0.685
10 out of 17 patients.	0.760
10 out of 18 patients.	0.676
11 out of 19 patients.	0.748
11 out of 20 patients.	0.668

The table below shows the operating characteristics of this monitoring rule for the study. The results are based on 5000 simulated studies for each scenario.

Assumed true risk not feasible	Percent of times the study stops for lack of feasibility	Average sample size
0.05	0.1%	20.0
0.10	0.8%	19.9
0.15	2.6%	19.6
0.20	6.3%	19.1
0.25	12.2%	18.2
0.30	18.0%	17.4
0.35	28.8%	16.0
0.40	40.7%	14.6
0.45	54.1%	12.9
0.50	67.5%	11.2
0.55	79.5%	9.6
0.60	88.3%	8.3
0.65	94.3%	7.1
0.70	98.2%	6.2
0.75	99.6%	5.7

10.6 Analysis of secondary endpoints

We will analyze progression-free survival by comparing the treatments via the logrank test. We will also estimate progression-free and overall survival probabilities using the Kaplan-Meier method. Toxicities will be categorized for azacitidine/entinostat and for Nivolumab, by frequency and type, and reported in tabular form. All patients will be evaluable for toxicity from the time of their first treatment with any study therapy.

10.7 Data Safety, Monitoring and Between Site Communication

As this is a multi-institutional study, there will be ongoing communications between sites. This includes site initiation visits, weekly telephone conferences and encrypted electronic communications. All data will be stored electronically on CRMS. All biologic samples will be held in a central location and overseen by study staff.

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES – Please see lab manual for full details.

Serial assessment for a series of correlative science parameters will be performed. These reflect, from pre-clinical studies including use of the epigenetic therapy agents in mouse models of NSCLC, our latest appreciation of epigenetic therapy induced changes that are predicted to potentially improve the efficacy of nivolumab[20]. These include target gene DNA methylation status in circulating DNA and in pre- and post-tumor biopsies, DNA exome sequencing to assess mutational burden and status of deriver gene mutations, genome wide and target gene DNA methylation levels, RNA-seq analyses of genome wide gene expression for detection of drug induced changes in endogenous retroviral (ERV) transcripts, transcripts for genes in a viral defense signaling pathway which drives Type 1 interferon responses which in turn increase PD-L1 expression, antigen presentation, and cytokine production. These expression studies also assess levels of CMYC, and key target genes which have a direct, positive relationship to tumor proliferation and immune evasion status. The biopsy expression studies also allow for detection of a transcriptional profile for immune exhaustion in subsets of immune cells and especially CD8 cells in the tumor microenvironment. Serial samples of blood mononuclear cells, will be assessed for immune exhaustion versus activation status with many of the above assays and serial plasma samples are collected to assay levels of key cytokines.

11.1 Plasma

Plasma samples will be obtained at timepoints indicated in the study calendar. Quantitative candidate promoter methylation analysis will performed on *APC*, *HCAD*, *p16*, *RASSF1A*, *GATA4*, as well as *Actin*.

Pre- and post-epigenetic therapy plasma will be tested by chemokine array which will analyze circulating chemokine ligands and receptors, specific interleukins and associated gene products such as TNF and MMP, as well as other immunomodulatory effects.

11.2 Tumor

Baseline tumor biopsy is required and will be analyzed in all subjects. Tumor biopsy while on epigenetic therapy and at progression are required for all Arms. These are detailed in the patient calendars found in **Section 8**.

As many of the following studies will be performed as tissue availability allows:

- Immunohistochemical (IHC) staining of tumor samples for PD-L1 infiltrating immune cell subsets (CD3, 4, 8, 20, 68), as well as other immune markers using both IHC or ISH.
- Laser capture microdissection, or macrodissection, followed by qRT-PCR and whole-genome microarray for pre- and post-treatment gene expression profiles related to immunological pathways.
- Quantitative candidate promoter methylation analysis: *APC*, *HCAD*, *p16*, RASSF1A, *GATA4*, *Actin*
- RNA Sequencing for human endogenous retrovirus (ERV) pathways known to be related to epigenetic therapies.
- Mutation, translocation, and amplification analysis of known biologically relevant driver mutations in non-squamous NSCLC to include: *EGFR*, *KRAS*, *EML4-ALK*, *BRAF*, *PIK3CA*, and *ERBB2* overexpression

11.3 Peripheral Blood Mononuclear Cells (PBMCs)

Baseline PBMCs will be analyzed as well as PBMCs following two cycles of therapy, prior to the third cycle (ie/between week 4 of Cycle 2 and week 1 of cycle 3).

Pre- and post-epigenetic therapy PBMCs will be evaluated for Cytokine expression, epigenetic status of cytokine promoters, and induction of responses to tumor antigens as well as other immunologic evaluations.

11.4 Analysis

To assess pharmacodynamic effects in samples obtained from subjects on each treatment arm, summary statistics for biomarkers of immunoregulatory activity and their corresponding changes (or percent changes) from baseline will be tabulated. Possible associations between changes in biomarker measures of interest and exposure to drug will be explored graphically. The frequency of significant demethylation and acetylation will be summarized in both treatment arms. The difference between the methylation indices post- and pre-treatment will be compared using paired Student's t-test. Similar analyses will be performed for other biomarker parameters. Relationships between changes in gene re-expression and other correlates with clinical response will be assessed using the Mantel-Haenszel test. In addition, estimates of the variance in the biological correlative parameters will be made in this group to be used in planning the integration of these studies in future trials.

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