TITLE: A Randomized Phase II Trial of Cytotoxic Chemotherapy with or without Epigenetic Priming in Patients with Advanced Non-Small Cell Lung Cancer

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NCI Supplied Agent:
Entinostat (IND #117931; NSC #706995) Syndax Pharmaceuticals, Inc.
5-azacitidine for injection (IND #117931; NSC 102816) Celgene Corporation
CC-486 (oral azacitidine) (IND #117931; NSC 102816) Celgene Corporation

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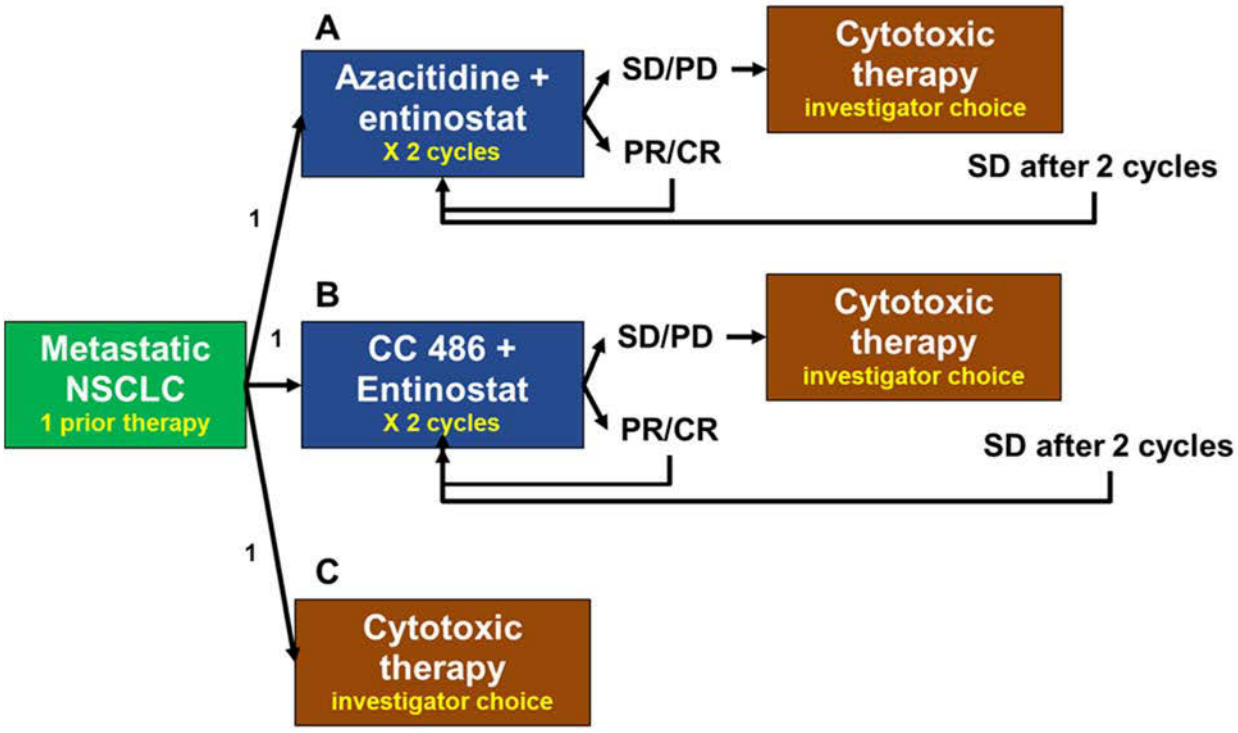
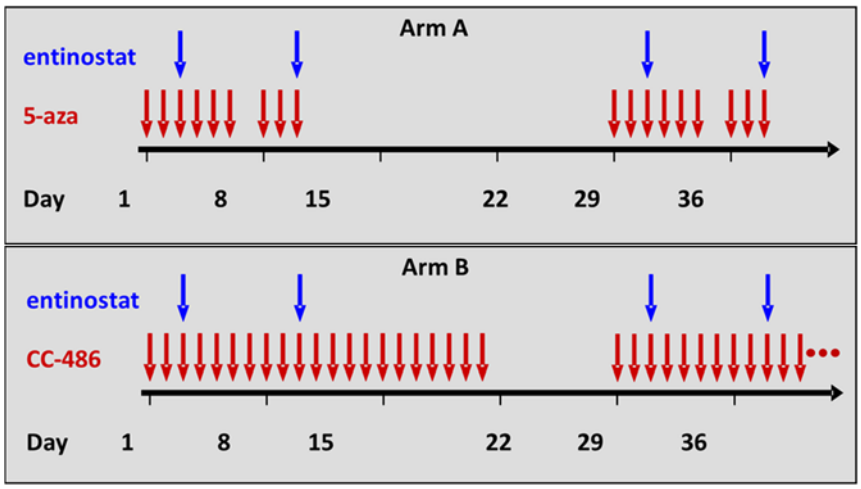
SCHEMA



Treating physician will choose the chemotherapy for each subject. Patients will then be randomized, stratified by chosen chemotherapy, to receive chemotherapy alone (Arm C), chemotherapy preceded by azacitidine 40 mg/m^2/day subcutaneous days 1-6 and 8-10 and entinostat 7mg PO days 3 and 10 on a 28 day cycle (Arm A), or CC486 300 mg PO days 1-21 and entinostat 7 mg PO days 3 and 10 on a 28 day cycle (Arm B).



Chemotherapy will consist of the treating oncologist's choice from 4 single agent regimens, including:

- irinotecan 300mg/m^2 IV once every 3 weeks
- docetaxel 75mg/m^2 IV once every 3 weeks
- gemcitabine 1000g/m^2 IV days 1 and 8 of a 3 week cycle
- pemetrexed 500 mg/m^2 IV once every 3 weeks (for non-squamous histology only)

Patients randomized to no epigenetic priming (Arm C) will receive chemotherapy immediately. Patients randomized to epigenetic priming (Arms A and B) who experience partial or complete response (PR or CR) after 2 cycles will be allowed continue epigenetic therapy until disease progression. Patients randomized to epigenetic priming (Arms A and B) who experience stable or progressive disease (SD or PD) after 2 cycles of induction, or progress before completing 2 cycles, will proceed to cytotoxic therapy. All patients may continue on cytotoxic therapy until PD with the following exception: those with SD after 2 cycles of epigenetic priming and SD after the first 2 cycles of cytotoxic therapy will receive an additional 2 cycles of epigenetic priming, followed by re-initiation of cytotoxic therapy. Patients receiving additional priming who experience PR or CR will continue azacitidine and entinostat until progression. Patients receiving additional priming who experience SD or PD will proceed to cytotoxic therapy.

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1. OBJECTIVES

1.1 Primary Objectives

1) Percentage of patients progression-free at 6 months from time of randomization

   Disease status at six months will be compared to disease status at time of randomization, and response coded based on RECIST 1.1 criteria. (Note: interim scans between baseline and the 6 month assessment will be used for clinical decision making as defined in the protocol, but not for assessment of this primary endpoint.)

1.2 Secondary Objectives

1) Progression Free Survival

   Progression-free survival (PFS) will be measured from the time of randomization until progressive disease or death. (Note: all scans will be used in assessment of this endpoint).

2) Overall Survival

   Overall Survival (OS) will be measured from the time of enrollment to trial until death.

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the most common cause of death from malignancy in both men and women. An estimated 157,300 people in the United States died from lung cancer in 2010.[1] Most non-small cell lung cancer patients present with advanced disease. Metastatic disease is typically treated with chemotherapy alone and is considered incurable with current therapy. There are many FDA-approved and compendia listed therapies for recurrent NSCLC, including all four of the chemotherapy options allowed in this protocol. Despite the variety of therapies, overall survival for NSCLC remains poor. New, effective therapies and strategies for lung cancer are a critical need.

2.2 CTEP IND Agents

2.2.1 **Azacitidine**

DNA methyltransferase inhibitors have been under investigation for over 25 years. The most widely used DNA methyltransferase inhibitor is 5-azacitidine.[2] This compound is a cytidine analogue that functions as a mechanism-dependent suicide inhibitor of DNA methyltransferases especially DNMT1. The active metabolite of

5-azacitidine needs to be incorporated into DNA. DNA methyltransferases

recognize 5-azacitidine as natural cytosine and initiate the methylation reaction. However, the 5-azacitidine prevents the completion of the methylation reaction. The DNMT1 enzyme becomes trapped and degraded.[3] 5-azacitidine has proven to be effective in a phase III clinical trial and has recently gained Food and Drug Administration approval for the treatment of myelodysplastic syndrome.[4]

Azacitidine in Lung Cancer

5-azacitidine has been studied in several phase I trials. Between 1973 and 1977, at least nine clinical studies of solid tumor patients (sample size between 8 and 177) treated with 5-azacitidine were performed that included a total of 78 lung cancer patients.[5] A variety of doses and regimens (intravenously or subcutaneously) were studied, with overall modest or no benefit. In the largest of these, 1 of 24 lung cancer patients had a partial remission which was transient. In 1987, another demethylating azaribonucleoside, 5,6-dihydroxy-azacitidine (DHAC) was first investigated in a phase II study in patients with extensive, untreated NSCLC.[6] It was given as a continuous infusion over five days and repeated every 21 days. Five out of 17 patients had disease stability of 2 or more months. Since 1984, at least six clinical phase I/II studies of solid tumor patients treated with decitabine were performed that included more than 50 lung cancer patients. Momparler et al. published their trial of decitabine in patients with metastatic lung cancer.[7,8] Median survival was 6.7 months, with three patients surviving more than 15 months. Major toxicities were hematopoietic, requiring 5–6 weeks recovery before repeat of treatment.

Oral Azacitidine (CC-486)

Oral azacitidine entered clinical testing in 2006 in subjects with MDS, CMML, and AML. The AZA PH US 2007 CL 005 study has shown that oral azacitidine is bioavailable and produces cumulative exposures (area under the concentration curve [AUC]) that are 30 to 60% of the exposure achieved with the labeled dose and schedule of Vidaza®. A MTD of 480 mg daily for 7 days was defined based on dose-limiting diarrhea at 600 mg [36]. The second part of the AZA PH US 2007 CL 005 study went on to explore both daily and twice-daily extended dosing schedules of 14 and 21 out of 28 days in a non-crossover fashion. Daily doses of 300 mg have proven to be tolerated on both the 14 and 21 out of 28 day schedules with myelosuppression, GI symptoms, and fatigue being the most common toxicities.[36] Subjects treated with oral azacitidine for 21 days had DNA hypomethylation that persisted through the end of cycle. This contrasts with the lack of persistent hypomethylation at the end of cycle when treated with oral azacitidine for only 7 days, thus providing mechanistic support for treating beyond 7 days. In summary, oral azacitidine is biologically active, reducing DNA methylation when administered at low doses on extended schedules.

In December, 2011, a Phase 1b study of CC-486 (AZA-ST-001) began enrolling subjects with relapsed or refractory solid tumors. In this safety study, patients are assigned at the investigator's discretion to one of 3 arms:

- Arm A: escalating doses of CC-486 days 1 to 14 out of 21 day schedule in combination with carboplatin (AUC = 4) on day 8 every 21 days.
- Arm B: escalating doses of CC-486 days 1 to 14 out of 21 day schedule in combination with Abraxane® 100 mg/m^2 days 8, 15 and 21
- Arm C: escalating doses of CC-486 days 1 to 21 out of 21 day schedule

Approximately 18 patients have completed at least on cycle of treatment on this study. There have been 4 Dose Limiting Toxicities (DLTs) to date at the 200 mg dose level of CC-486: 2 on Arm B and one each on Arms A and C. All 4 DLTs were neutropenia, 2 were febrile neutropenia (one on Arm B and one on Arm C) and 2 were delay to the start of Cycle 2 due to an Absolute Neutrophil Count < 1.5 X 10^9/L (one on Arm B and one on Arm A). Arm B has since been amended to eliminate the day 21 dose of Abraxane®. The study is continuing to enroll and a MTD has not yet been defined.

2.2.2 **Entinostat**

Histone deacetylases (HDACs) are important in the regulation of gene expression and in the field of target-specific anticancer drug development.[9-11] HDACs deacetylate histones which leads to repression of gene transcription. Eight HDACs have been identified in mammalian cells. Beside specific subcellular localization and distinct tissue expression patterns, different HDACs have been shown to associate with distinct transcription regulatory complexes.[12-14] A number of HDAC inhibitors can induce differentiation, growth arrest, and/or apoptosis of tumor cells in vitro.[11,15-24] Some have been shown to inhibit growth of cancer cells in animal models.[11,25-28] A smaller number of these are apparently nontoxic to the host and possibly target tumors selectively.[11,29]

Entinostat in Lung Cancer

A phase I clinical trial has been conducted using entinostat in advanced solid tumors. Of the 31 patients enrolled, four of them had NSCLC.[30] One NSCLC patient required two dose reductions from the 10 mg/m2 dose cohort, but also had disease stabilization for 9 months. Another NSCLC patient had stable disease after two cycles but during the fourth cycle opted to change to standard therapy before disease assessment could be made. The main side effects included hematologic and gastrointestinal toxicities.

2.2.3 Pre-clinical Use of DNMT and HDAC Inhibitor Combinations

The use of DNMT and HDAC inhibitors as single agents in patients with solid tumors has been slowed by toxicity at doses required to achieve reversal of

methylation. An observation by Cameron and colleagues may change the utility of these agents in solid tumors.[31] This study showed that the methylation pattern of colon cancer cell lines was modulated in a synergistic fashion when treated with DNMT and HDAC inhibitors in combination.

Further studies have been performed in lung cancer cell lines. One study assessed the combination of decitabine with either depsipeptide or trichostatin A. This study documented enhanced apoptosis in the cell lines treated with the combination as compared to an HDAC inhibitor alone.[32]

The combination of DNA methyltransferase inhibitors has been assessed in a lung cancer animal model. Decitabine and phenylbutyrate were studied in the preventative setting in mice. Mice treated with decitabine had 30% fewer tobacco-carcinogen induced lung cancers. Mice treated with decitabine and phenylbutyrate had over 50% fewer tobacco-carcinogen induced lung cancers. These data in pre-clinical models are encouraging for the use of these classes of agents in patients.[33]

2.2.4 Clinical Use of DNMT and HDAC Inhibitor Combinations in Hematologic Malignancies

DNMT and HDAC inhibitors are currently being studied in combination in hematologic malignancies. A phase I clinical trial assessing the use of 5-azacitidine and phenylbutyrate in myelodysplasia was recently published.[34] In this study 11 of 29 patients treated had clinical responses. Response was highly correlated with reversal of previously aberrantly methylated genes in myelodysplasia. The biggest drawback of this combination was the need for continuous infusion of phenylbutyrate.

A phase I clinical trial recently completed at Johns Hopkins assessing the combination of entinostat and 5-azacitidine in myelodysplasia. To date in this study, 14 of 19 evaluable patients have responded, including 2 complete remissions (Gore, unpublished data). Several of the responses continue to improve over time (for example, hematologic improvement progressing to partial response). Responses have been seen across dose cohorts.

2.2.5 Clinical Use of Azacitidine and Entinostat in Lung Cancer

We have recently completed the first combination study of azacitidine and entinostat in patients with metastatic lung cancer.[35] This study defined a regimen of azacitidine 40 mg/m2 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. Remarkably, although this population was heavily pretreated (with progressive disease after a median of three prior regimens for metastatic disease), major objective responses were observed, including a complete response, a partial response with complete resolution of multiple liver metastases, and several patients with durable stable disease. Median

overall survival in an intent-to-treat analysis (including all patients enrolled on study) was 6.4 months, comparing favorably with any available therapy for this patient population.

2.3 Standard Cytotoxic Agents (No CTEP IND)

2.3.1 Docetaxel

Docetaxel is an FDA approved therapy for single agent treatment in the second line for NSCLC. Docetaxel is an anti-mitotic chemotherapy. The molecule reversibly binds and stabilizes microtubules and prevents depolymerization. Docetaxel is administered intravenously as a bolus dosed at 75 mg/m2 every 3 weeks. The drug is metabolized by cytochrome p450 CYP3A4 and CYP3A5 isoenzymes

2.3.2 Gemcitabine

Gemcitabine in combination with cisplatin is an FDA approved therapy for first line therapy in inoperable NSCLC. It is frequently used as a single agent in the second line setting. Gemcitabine is a nucleoside analog chemotherapy. Gemcitabine, when incorporated into DNA, blocks replication to exert its anti-neoplastic activity. Gemcitabine is administered intravenously as a bolus dosed at 1000 mg/m2 on days 1, 8, and 15 of a 28 days cycle. Gemcitabine has no indication for dose adjustments based on renal or hepatic impairment.

2.3.3 Irinotecan

Irinotecan is an NCCN compendia listed agent for single agent use in the second line for NSCLC. Irinotecan is a topoisomerase I inhibitor which subsequently inhibits DNA replication and transcription. Irinotecan is administered as an intravenous bolus on day one of a 21 day cycle at a dose of 300 mg/m2. Major drug metabolism occurs through p450 CYP2B6 and CYP3A4, P-Glycoprotein, SLCO1b1, and UGT1A1 and dose reductions are recommended in the setting of hepatic impairment.

2.3.4 Pemetrexed

Pemetrexed carries an FDA approval for therapy as single agent treatment in the second line for NSCLC. Pemetrexed is a folate analog that work by inhibiting purine and pyrimidine synthesis and prevents DNA and RNA formation. Pemetrexed is administered as an intravenous bolus on day one of a 21 day cycle at a dose of 500 mg/m2. Use is not recommended in patient with creatinine clearance < 45 mL/minute. Dose reductions are recommended in the setting of transaminitis.

2.4 Rationale for Epigenetic Priming of Chemotherapy

Epigenetics in Cancer

Both genetic and epigenetic alterations play central roles in tumorigenesis.[37,38] Aberrant DNA methylation and aberrant histone acetylation represent two of the critical mechanisms of tumor-specific epigenetic alterations. Through these epigenetic changes, tumor-suppressor genes can be aberrantly "silenced," promoting dysregulated cell growth. 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.[31,39]

Epigenetics and Chemotherapeutic Resistance in Lung Cancer

Approximately 20 - 25% of advanced non-small cell lung cancer patients respond to initial therapy with platinum containing paclitaxel doublets. However, response rates to subsequent single or double agent regimens for recurrent and progressive disease are poor, typically in the range of 9 - 10%.[40] Erlotinib is the only agent approved for use after second-line therapy in lung cancer, with a demonstrated response rate of 8.9% in patients with one or two prior therapies.[41] Mechanisms of resistance accounting for the progressively unresponsive nature of these tumors have not been fully defined.

Recent data suggests that epigenetic mechanisms are essential to the maintenance of a subpopulation of drug-resistant tumor cells, even in tumors highly susceptible to targeted therapeutics.[42] Using four different HDAC inhibitors, including entinostat, Sharma et al. were able to prevent persistence of a drug-tolerant population. These data suggest that reversal of epigenetic gene silencing could represent a means of increasing the efficacy of treatments with known activity in lung cancer.

Clinical observations from lung cancer patients treated with the combination of azacitidine and entinostat

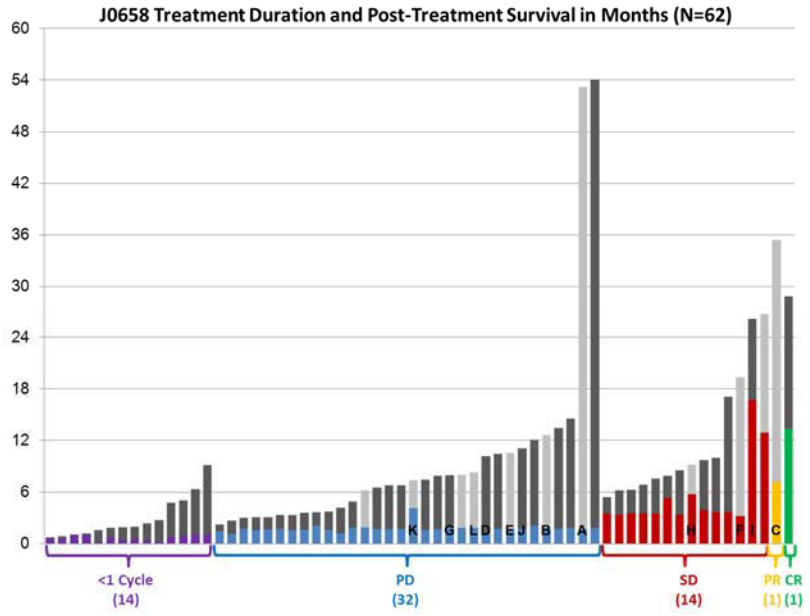
An intriguing observation from our completed study of the combination of azacitidine and entinostat in non-small cell lung cancer concerned the response to the immediate subsequent therapy following disease progression on study. Given the advanced state of disease and the number of prior therapies given, the duration of survival post-epigenetic therapy in many patients on this study was surprising (Figure 3A). Median survival among patients who completed at least one cycle of epigenetic therapy was 8.6 months (95% CI 5.5 – 12.2) and includes ongoing long-term survivors of 44 and 52 months post-epigenetic therapy, both having received only one post-study treatment regimen. A total of 19 patients received at least one subsequent systemic treatment in the 6 months after going off study. Interestingly,

four of the patients who received subsequent chemotherapy (21%) had major objective responses to the immediate subsequent therapy (Figure 3B). These data, while preliminary, support the hypothesis that combination epigenetic therapy may improve the responsiveness of lung cancer to subsequent cytotoxic therapies. Testing this concept, epigenetic priming as a strategy to sensitize tumors to cytotoxic therapy, is the primary goal of the current proposal.

Several cases of major objective response observed here are of interest. One is a man who had previously experienced disease progression on carboplatin, paclitaxel, and bevacizumab. Following epigenetic therapy, he was given a similar regimen: cisplatin, docetaxel, and bevacizumab. Remarkably, he has experienced a rapid and durable response, with a 90% reduction in tumor by RECIST 1.1 criteria as well as normalization of elevated CEA. Representative images are shown in Figure 4.

Additional recent clinical data in support of epigenetic priming

Emerging data from clinical studies in multiple tumor types supports the hypothesis that epigenetically targeted therapy may sensitize to subsequent cytotoxic therapy. A recent study in platinum-resistant ovarian cancer patients explored the demethylating agent decitabine days 1 – 5 followed by carboplatin on day 8.[43] Of 17 patients treated, 6 objective responses (1 CR, 5PR; RR = 35%) were observed. Overall clinical benefit rate was 70%, and median progression-free survival was over 300 days.



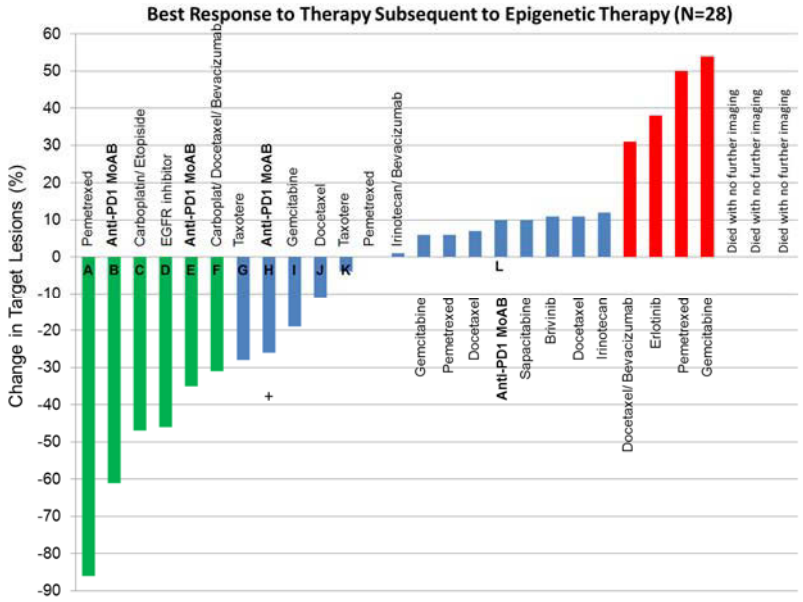


Figure 3: Survival, subsequent therapies, and response. A. Duration of survival on and after protocol therapy. The height of the gray bar indicates duration of survival. Light gray bars indicate patients who are still alive. The colored portion of the bar represents the duration of therapy received on trial. NE: non-evaluable for response, PD: progressive disease, SD: stable disease, PR: partial response, CR: complete response. If a patient received subsequent chemotherapy within 6 months, it is listed above the patient's survival bar. Letters identify corresponding patients in panel B**. B. Waterfall plot of response to immediate subsequent therapy.** Best change in defined target lesions to subsequent systemic anti-cancer treatment following epigenetic therapy is shown. Green: PR, blue: SD, red: PD. Three patients, indicated at right, died without follow-up imaging.

A recent randomized phase II study in hormone-refractory ER-positive breast cancer evaluated exemestane with or without entinostat, seeking to restore hormonal sensitivity (unpublished data). This study has met its predetermined statistical endpoint of progression free survival improvement, 4.28 vs. 2.27 months (Hazard Ratio= 0.73, p=0.06) and a phase III trial of the same concept is being planned.

Finally, a clinical trial was recently reported using epigenetic priming prior to standard therapy in patients with AML.[44] This study explored multiple schedules of decitabine prior to standard AC in less-than-favorable risk AML, demonstrating a 90% response rate including 57% CR. Interestingly, of the 10 patients with PR, 8 achieved CR in response to their next therapy, raising the total CR rate to 83%.

Together these studies offer strong preliminary data suggesting that epigenetic therapy, by reactivating silenced target genes in cancer, may enhance the efficacy of subsequent therapy. We believe that it is time for this concept to be formally tested in a carefully designed randomized clinical study. The clinical trial proposed in this concept will build on our initial CTEP-supported clinical trial data in metastatic lung cancer to rigorously test the idea that epigenetic therapy can augment the clinical utility of

cytotoxic therapy in patients with advanced disease.

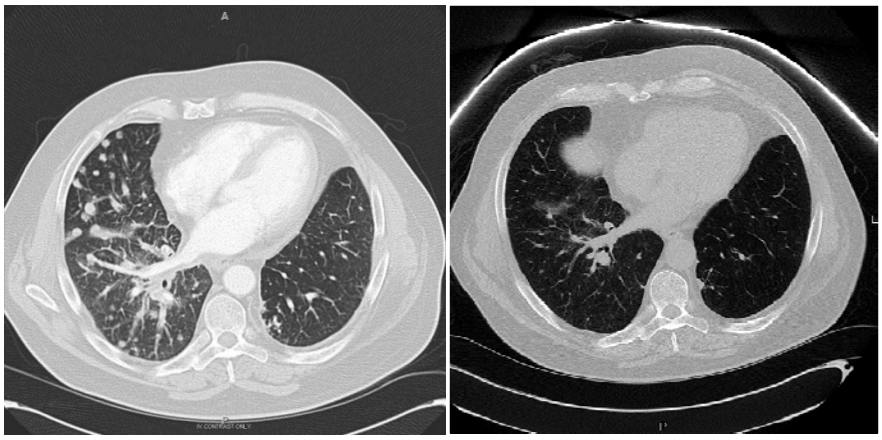


Figure 4. Response after epigenetic priming. A CT scans of a patient who received four cycles of epigenetic therapy, who had previously progressed on carboplatin, paclitaxel, and avastin. Images on the left show multiple persistent lung masses after epigenetic therapy. Images on the right show disease response after four cycles of cisplatin, docetaxel, and avastin.

Summary

We have demonstrated that azacitidine plus entinostat has remarkable activity in a small group of lung cancer patients. Additionally, our data suggest an entirely different potential benefit from the same drug combination, namely increasing efficacy of more standard anticancer therapies. Recent emerging data from other groups suggest that this mechanism may apply in multiple cancer types. We will formally test the epigenetic priming concept in this study of patients with non-small cell lung cancer.

2.5 Correlative Studies Background

We had previously defined methylation status of 4 key genes (*CDKN2a*, *CDH13*, *APC*, and *RASSF1a*) in tumor and histologically normal mediastinal lymph nodes as a strong prognostic factor in patients with early stage non-small cell lung cancer.[45] Patients with promoter methylation of at least 2 of these 4 genes in tumor and mediastinal lymph nodes had a markedly increased likelihood of early disease recurrence. Our group had also demonstrated several years ago that tumor-specific methylation changes are detectable in circulating tumor DNA of lung cancer patients.[46] Combining these lines of research, we quantitatively assessed methylation status of these 4 genes in circulating DNA from patients treated with azacitidine and entinostat. We found that patients with detectable methylation of at least 2 of these 4 genes at baseline demonstrating demethylation in the first month of epigenetic therapy had significantly improved progression-free ($p = 0.034$) and overall survival ($p = 0.035$; Figure 2). This represents a potential blood-based biomarker defining a subset of patients that may selectively benefit from combinatorial epigenetic therapy. The proposed trial design offers an opportunity to validate this biomarker prospectively, by examination of this panel at baseline and after 1 month of therapy, both in patients receiving epigenetic therapy

AND, as an important control for the specificity of this biomarker, in patients receiving cytotoxic chemotherapy. This is a key secondary goal of the proposed study.

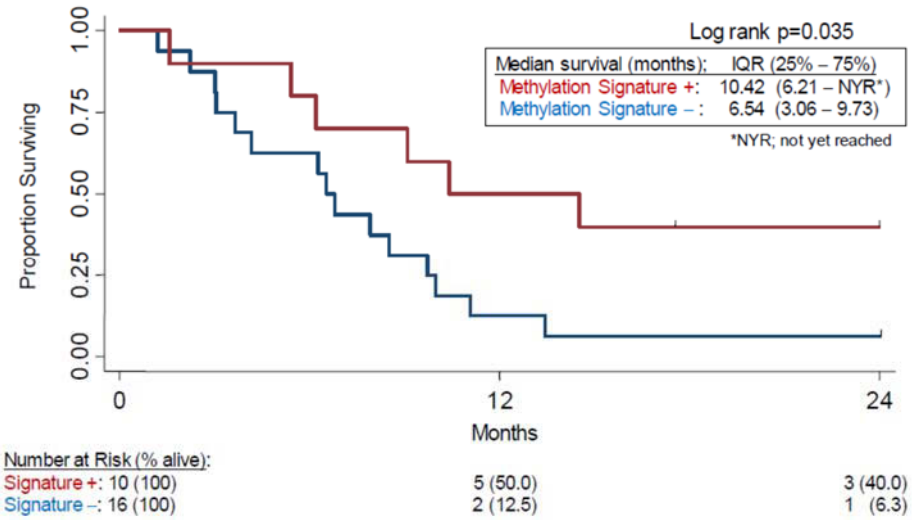


Figure 2. Kaplan-Meier analysis of survival by target gene demethylation. Promoter methylation of *APC*, *CDH13*, *RASS1a*, and *CDKN2A* were evaluated in circulating plasma DNA from patients, pre-treatment and on day 29. Red: patients with methylation of ≥2 of these 4 genes pre-treatment that demonstrate demethylation by day 29. Blue: all other patients with detectable circulating DNA (total N = 26).

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically proven non-small cell lung cancer. Tumor tissue must be available from all patients prior to initiation of protocol therapy, either from original diagnostic biopsy, or biopsy performed prior to initiation of protocol therapy.

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.

3.1.3 Patients must have received 1 prior platinum containing doublet regardless of mutation status

3.1.4 Patients with targetable mutation i.e. EGFR or ALK, must have been treated with at least 1 prior TKI.

3.1.5 Prior immunotherapy is allowed. Do not feel tyrosine or targeted therapies have effects on immunotherapy; erlotenib is approved for patients without mutations in 3rd line setting. We have tried to clarify this because we are testing this for patients with targetable mutations. We feel that with the evolving field of targetable mutations approval of ALK and EGFR therapy

in near future we want to be able to allow more than 1 prior TKI. Prior Immunotherapy is allowed as we do not want to restrict patient eligibility regarding immunotherapy since not all patients are eligible to receive immune including those with hx of auto immune dx or those with interstitial lung disease. Maintenance chemo therapy does not count as line of chemo.

3.1.6 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of azacitidine or entinostat alone or in combination with irinotecan, gemcitabine, pemetrexed, or docetaxel in patients <18 years of age, children are excluded from this study.

3.1.7 ECOG performance status 0 or 1 (Karnofsky ≥70%, see Appendix A).

3.1.8 Life expectancy of greater than 12 weeks.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– creatinine	within normal institutional limits
OR	
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.10 The effects of entinostat and azacitidine 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. 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.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 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 4 weeks earlier.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with uncontrolled brain metastases. Patients with brain metastases must have stable neurologic status following local therapy (surgery or radiation) for at least 4 weeks, and must be without neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients may be treated with steroids as clinically indicated.

3.2.4 Patients with liver metastases that replace greater than 30% of the liver parenchyma.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to entinostat, azacitidine, mannitol, irinotecan, docetaxel, Pemetrexed, or gemcitabine, or other agents used in the study.

3.2.6 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, NYHA class 3-4 congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because entinostat, azacitidine, and irinotecan, docetaxel, Pemetrexed, or gemcitabine 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 irinotecan, docetaxel, Pemetrexed, or gemcitabine breastfeeding should be discontinued if the mother is treated on this protocol. These potential risks may also apply to other agents used in this study.

3.2.8 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with entinostat, azacitidine, or irinotecan, docetaxel, Pemetrexed, or gemcitabine. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

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

Table 1. Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	63	+	97	=	160
Ethnic Category: Total of all subjects	65 (A1)	+	100 (B1)	=	165 (C1)
Racial Category					
American Indian or Alaskan Native	2	+	0	=	2
Asian	6	+	8	=	14
Black or African American	11	+	15	=	26
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	46	+	77	=	123
Racial Category: Total of all subjects	65 (A2)	+	100 (B2)	=	165 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

4 REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center by the Study Coordinator. The JHU Data Manager will notify The Johns Hopkins Oncology Center Central Registration Office (410-955-8271) of each patient entered on study. All sites should call the JHU Data Manager at 410-550-2751 to verify agent availability.
Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The JHU Data Manager should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) (except for Group studies).

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed 410-550-0675 or scanned and emailed jrober31@jhmi.edu(Appendix D):

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form

The research nurse or data manager at the participating site will then call 410-550-2751 to verify eligibility. To complete the registration process, the following will occur:

- assignment of a patient study number
- registration of the patient on the study
- fax or e-mail of the patient study number and dose to the participating site
- notification of the research nurse or data manager at the participating site to verbally confirm registration.

5 TREATMENT PLAN

5.1 Agent Administration

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.

Upon enrollment, the treating physician will choose an appropriate cytotoxic agent for the individual patient, and randomization will be stratified by the agent. Patients will then be randomized to one of three study arms.

The epigenetic priming phase of the study will proceed as follows. On Arm A, patients will receive 2 cycles of azacitidine 40 mg/m2/day SC days 1-6 and 8-10 and entinostat 7mg PO days 3 and 10 of a 28 day cycle. On Arm B, patients will receive 2 cycles of CC-486 300 mg PO days 1-21 and entinostat 7mg PO days 3 and 10 of a 28 day cycle. On Arm C, patients will not receive epigenetic priming, and instead will proceed directly to cytotoxic therapy. If patients on Arms A or B have a PR or CR at the end of Cycle 2, they may continue epigenetic therapy until disease progression, at which time they will proceed to cytotoxic therapy. All other patients will proceed to cytotoxic therapy after 2 cycles of epigenetic therapy (or fewer, if unable/unwilling to complete the full 2 cycles).

In all 3 arms, in the cytotoxic therapy phase of the study, patients will receive the previously assigned cytotoxic agent. In arms A and B, if the patient has SD after 2 cycles of epigenetic therapy and SD after 2 cycles of cytotoxic therapy, they will be re-primed with an additional 2 cycles of epigenetic therapy, as described in the preceding paragraph, with the same rules for staying on epigenetic therapy or proceeding to cytotoxic therapy. Only one “re-priming” will be allowed in any patient on study. Patients may stay on cytotoxic therapy until PD, unacceptable toxicity, or a decision by the patient or the treating physician to stop therapy.

Table 2. Agents Used

Agents	Premedication	Dose	Route	Schedule	Cycle Length
Epigenetic priming					

Entinostat	5HT3 inhibitor orally or IV 30 minutes prior to entinostat; take on am empty stomach, at least 1 hour before or 2 hours after a meal, avoid stomach acid-suppressing medications	7mg	PO	Days 3 & 10	28 days
Azacitidine	5HT3 inhibitor orally or IV 30 minutes prior to injection with azacitidine; Rotate site of injection	40 mg/m^2	SC	Days 1-6, 8-10	
CC-486	Subjects should drink 8 ounces (240 mL) of room temperature water with each dose. Oral azacitidine may be taken on an empty stomach or with food.	300 mg	PO	Day 1-21	
Cytotoxic therapy					
Irinotecan	Dexamethasone 12 mg orally or IV; 5HT3 orally or IV; both medications 30 minutes prior to irinotecan; Atropine 0.25 mg subcutaneously prn q2 hours for cholinergic reaction; loperamide 4 mg with first onset of diarrhea then 2 mg every 2-4 hours around the clock until diarrhea free for at least 12 hours; Dexamethasone 8 mg OR 5HT3 orally on days 2-4 post chemotherapy.	300 mg/m^2	IV	Day 1	21 days
Docetaxel	Dexamethasone 8 mg orally every 8 hours for three doses the day prior to chemotherapy; Dexamethasone 8 mg orally every 8 hours for three doses starting the evening of chemotherapy administration.	75 mg/m^2	IV	Day 1	
Pemetrexed	Dexamethasone 4 mg orally twice daily the day before, day of, and day after chemotherapy; Folate 1 mg orally for 7 days prior to first dose of chemo and continuing 21 days after chemo; B12 1gm IM 1 week prior to first dose of chemo and every 8-9 weeks while receiving chemo continuing until 3 weeks after last dose of pemetrexed.	500 mg/m^2	IV	Day 1	
Gemcitabine	Dexamethasone 12 mg orally or IV days 1, 8, and 15 of each cycle; Dexamethasone 12mg orally or IV 30 minutes prior to doses of gemcitabine.	1000 mg/m^2	IV	Days 1 and 8	

5.1.1 **Epigenetic Modifying Agents**

5.1.1.1 Entinostat

Entinostat is an oral agent. Entinostat should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. The tablets should be taken one at a time. 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. Entinostat tablets should not be split, crushed, or chewed.

Entinostat absorption may be altered by drugs that reduce the acidity of the stomach. Proton-pump inhibitors should be avoided during the week on the study during which patients are receiving entinostat. H2-blockers and antacids should be avoided 24 hours prior to and following the time of entinostat administration.

5.1.1.2 5-Azacitidine (subcutaneous)

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 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.

5.1.1.3 CC-486 (oral azacitidine)

CC-486 (oral azacitidine) is supplied as 100 mg tablets for oral administration. Oral azacitidine should be stored in an area free of environmental extremes and must be accessible only to study personnel.

5.1.2 **Cytotoxic Agents**

5.1.2.1 Irinotecan

Irinotecan hydrochloride injection is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials containing 40 mg Irinotecan hydrochloride, and 5 mL-fill vials containing 100 mg Irinotecan hydrochloride. Each milliliter of solution contains 20 mg of Irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan hydrochloride injection is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

5.1.2.2 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N- *tert* -butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$• $3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Docetaxel is available in multiple concentrations and vial configurations. Consult specific product labels for preparation instructions and excipient information.

5.1.2.3 Pemetrexed

Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 100-mg or 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

5.1.2.4 Gemcitabine

Gemcitabine HC1 is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. The clinical formulation is supplied in a sterile form for intravenous use only. Vials of gemcitabine contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

5.2 General Concomitant Medication and Supportive Care Guidelines

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

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

5.2.3 GI Medications: Drugs used to reduce the acidity (increase pH) of the stomach, i.e. H2 antagonists, proton-pump inhibitors, antacids, etc., could potentially interfere with entinostat absorption. Proton-pump inhibitors should be avoided during the week in which patients are receiving entinostat. H2-blockers and antacids should be avoided 24 hours prior to and following the time of entinostat administration.

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

5.2.5 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 1-2, 4-6, and 8-9. 5HT3 inhibitor may also be taken for delayed nausea as needed.

5.2.6 Diarrhea: If diarrhea occurs during dosing, an anti-diarrheal agent(s) may be used.

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

5.2.8 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.

5.2.9 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.

5.2.10 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.

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

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- 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.

5.4 Duration of Follow Up

Once treatment has been discontinued, patients will be followed every 3 then 6 months, out to 24 months which is shown in the study calendar in section 10. After the 24 month visit the patient will be followed by phone once a year for survival or until death. We will routinely 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. Permission to obtain this data will be will be secured from the subject in the consent form.

5.5 Criteria for Removal from Study

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

5.5.1 Interruption of scheduled therapy for greater than two weeks.
5.5.2 Intolerable adverse effects that are judged by the investigator to be either physically or psychologically detrimental to the patient.
5.5.3 Patient decision to discontinue treatment.
5.5.4 Pregnancy.
5.5.5 Patient non-compliance.
5.5.6 Unresolved or recurrent Grade 3 or 4 toxicity.
5.5.7 Treatment with other chemotherapeutic or investigational anti-neoplastic drugs.
5.5.8 Radiation therapy to any lesion. The need for palliative radiation therapy will be considered progressive disease.
5.5.9 Disease progression.

6 DOSING DELAYS/DOSE MODIFICATIONS

Treatment will be modified based on toxicity as described below for all patients receiving entinostat and azacitidine.

6.1.1 Neutropenia:

- See Table 3 for dose adjustment criteria
- Filgrastim or pegfilgrastim may be used in accordance with ASCO guidelines
- If held, therapy should restart with appropriate dose adjustment in the following cycle if toxicity has resolved to ≤ Grade 2.

6.1.2 Thrombocytopenia.

- See Table 3 for dose adjustment criteria
- If held, therapy should restart with appropriate dose adjustment in the following cycle if toxicity has resolved to ≤ Grade 2.

6.1.3 Anemia.

- Hold epigenetic therapy for Grade 3 or 4 anemia according to guidelines in table 3.
- Erythropoietin or darbepoietin may be used to treat chemotherapy-induced anemia at the discretion of the treating physician.
- If held, therapy should restart with appropriate dose adjustment in the following cycle if toxicity has resolved to ≤ Grade 2.

6.1.4 Diarrhea

- Patients will be instructed to begin taking loperamide at the earliest signs of:
  (1) a poorly formed or loose stool,
  (2) occurrence of 1 to 2 more bowel movements than usual in one day, or
  (3) 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 (4 mg every 4 hours while asleep) around the clock until diarrhea-free for at least 12 hours. Additional anti-diarrheal measures

may be used at the discretion of the treating physician.
- If the measures above fail, the dose may be reduced as listed in Table 2.

6.1.5 Nausea/Vomiting
- Both entinostat and azacitidine use can lead to nausea and vomiting.
- Prophylactic 5-HT3 inhibitors will be used on days when both entinostat and azacitidine will be administered
- Prophylactic 5HT5 inhibitor will be used first-line on days when azacitidine is given alone or for delayed nausea and vomiting.
- If nausea and vomiting persists despite these measures, more aggressive use of 5-HT3 antagonists or other anti-emetics can be used at the discretion of the treating physician.

6.1.6 Metabolic/electrolyte abnormalities
- Entinostat is associated with multiple electrolyte abnormalities including hypermagnesemia, hyperglycemia, hypophosphatemia, hyponatremia, and hypocalcemia. Low values will be repleted as appropriate. Hyperglycemia will be corrected at the discretion of the treating physician.
- Entinostat will only be dose-reduced for grade 4 toxicities refractory to appropriate treatment.
- Hold epigenetic therapy for AST/ALT ≥ 3X upper limit of normal AND Bilirubin ≥ 2 x upper limit of normal.

6.1.7 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, treatment should be withheld until the toxicity resolves to grade 1 or less.
- If treatment is held or delayed for a non-hematologic toxicity not described above, both drugs should be dose-reduced (entinostat dose reduced to 4 mg, and azacitidine dose reduced by 10 mg/m2) unless the toxicity can be clearly attributed to entinostat or azacitidine specifically.

6.1.8 Dose Delays and Modification for Commercially Available Chemotherapies
- Dose delays and modifications for irinotecan, docetaxel, gemcitabine, and docetaxel will be made at the treating physician's discretion.

Table 3: Dose Reductions for azacitidine, CC-486, and entinostat

Toxicity	Grade	Azacitidine (SC)	CC-486 (PO)	Entinostat
Neutropenia	Grade 1 or 2	No change	No change	No change
	Grade 3	Hold and reduce next cycle by 10 mg/m^2	No change	No change

	Grade 4	Hold and reduce next cycle by 10 mg/m^2	Hold and reduce next cycle to 200 mg	Hold and reduce next cycle to 4 mg
Thrombocytopenia	Grade 1 (75-100)	No change	No change	No change
	Grade 2 (50-75)	No change	No change	No change
	Grade 3 or 4 (25-50; < 25)	Hold and reduce next cycle by 10 mg/m^2	Hold and reduce next cycle to 200 mg	Hold and reduce next cycle to 4 mg
Anemia	Grade 1 or 2	No change	No change	No change
	Grade 3	Hold and reduce next cycle by 10 mg/m^2	No change	No change
	Grade 4	Hold and reduce next cycle by 10 mg/m^2	Hold and reduce next cycle to 200 mg	Hold and reduce next cycle to 4 mg
Diarrhea (Reduce dose only after optimal use of loperamide)	Grade 1 or 2	No change	No change	No change
	Grade 3	Hold and reduce next cycle by 10 mg/m^2	No change	No change
	Grade 4	Hold and reduce next cycle by 10 mg/m^2	Hold and reduce next cycle to 200 mg	Hold and reduce next cycle to 4 mg
Nausea / Vomiting (Reduce dose only after optimal use of anti-emetics)	Grade 1 or 2	No change	No change	No change
	Grade 3 or 4	Hold and reduce next cycle by 10 mg/m^2	Hold and reduce next cycle to 200 mg	Hold and reduce next cycle to 4 mg

7 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 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via AdEERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for *5-azacitidine and CC-486*

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Azacitidine (NSC 102816)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited

reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1099 patients.* Below is the CAEPR for azacitidine.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 18, 2014[1]

Adverse Events with Possible Relationship to Azacitidine (CTCAE 4.0 Term) [n= 1099]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
	Heart failure		***Heart failure (Gr 2)***
	Pericardial effusion		***Pericardial effusion (Gr 2)***
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr 2)***
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		***Colitis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Esophagitis		***Esophagitis (Gr 2)***
	Gastrointestinal hemorrhage[2]		
	Hemorrhoids		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***

Fever			***Fever (Gr 3)***
Injection site reaction			***Injection site reaction (Gr 2)***
	Malaise		
	Non-cardiac chest pain		
	Pain		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
Infection[3]			***Infection[3] (Gr 4)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 4)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 2)***
Anorexia			***Anorexia (Gr 2)***
	Hypokalemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Lethargy		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
	Somnolence		***Somnolence (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		***Confusion (Gr 2)***
	Depression		
	Insomnia		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 2)***
Dyspnea			***Dyspnea (Gr 4)***
	Epistaxis		***Epistaxis (Gr 2)***
	Pharyngolaryngeal pain		
	Postnasal drip		***Postnasal drip (Gr 2)***
	Respiratory, thoracic and mediastinal disorders - Other (abnormal breath sounds)[4]		***Respiratory, thoracic and mediastinal disorders - Other (abnormal breath sounds)[4] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Purpura		***Purpura (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (skin lesion)		
VASCULAR DISORDERS			
	Hematoma		***Hematoma (Gr 2)***
	Hypotension		***Hypotension (Gr 3)***
	Vascular disorders - Other (pallor)		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Abnormal breath sounds includes rales and rhonchi.

Adverse events reported on azacitidine trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that azacitidine caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (splenomegaly); Bone marrow hypocellular; Leukocytosis
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac disorders - Other (cardiac valve vegetation); Chest pain - cardiac; Myocardial infarction; Palpitations; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Ventricular fibrillation
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
EYE DISORDERS - Eye disorders - Other (eye/conjunctival hemorrhage); Eye disorders- Other (retina hemorrhage); Papilledema; Uveitis
GASTROINTESTINAL DISORDERS - Abdominal distension; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Flatulence; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (inguinal hernia, obstructive); Gastrointestinal disorders - Other

(intestinal ischemia); Gastrointestinal disorders - Other (intussusception); Gastrointestinal disorders - Other (mouth/tongue/oral ulceration); Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (general weakness); General disorders and administration site conditions - Other (Sweet's Syndrome); General disorders and administration site conditions - Other (systemic inflammatory response syndrome); Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Burn; Fall; Hip fracture; Injury, poisoning and procedural complications - Other (excoriation); Postoperative hemorrhage; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (blood LDH increased); Investigations - Other (blood urea increased); Investigations - Other (cardiac murmur); Investigations - Other (protein total decreased); Lipase increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (fluid overload); Metabolism and nutrition disorders - Other (hypovolemia); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (chondritis); Musculoskeletal and connective tissue disorder - Other (intervertebral disc protrusion); Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (colonic polyp, vaginal polyp); Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dysesthesia; Dysgeusia; Hydrocephalus; Intracranial hemorrhage; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Seizure; Sinus pain; Syncope
PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Renal and urinary disorders - Other (calculus urinary); Renal calculi; Urinary frequency; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Reproductive system and breast disorders - Other (benign prostatic hyperplasia); Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Hypoxia; Nasal congestion; Pleural effusion; Pleuritic pain; Pneumonitis; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (Chronic Obstructive Pulmonary Disease); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Respiratory, thoracic and mediastinal disorders - Other (pharyngeal erythema); Respiratory, thoracic and mediastinal disorders - Other (pneumonia legionella); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (ecthyma gangrenosum); Skin and subcutaneous tissue disorders - Other (skin laceration); Skin and subcutaneous tissue disorders - Other (skin nodule); Skin induration; Urticaria
VASCULAR DISORDERS – Flushing; Hypertension; Thromboembolic event; Vasculitis; Visceral arterial ischemia

Note: Azacitidine in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Entinostat

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MS-275 (SNDX-275, entinostat, NSC 706995)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 215 patients.* Below is the CAEPR for MS-275 (SNDX-275, entinostat).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades

to determine if expedited reporting is required.

Version 2.4, February 13, 2013[1]

Adverse Events with Possible Relationship to MS-275 (SNDX-275, entinostat) (CTCAE 4.0 Term) [n= 215]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Non-cardiac chest pain		
INFECTIONS AND INFESTATIONS			

	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		
	Blood bilirubin increased		
	Creatinine increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
Hypoalbuminemia			***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 3)***
Hypophosphatemia			***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Generalized muscle weakness		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
Headache			***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
Dyspnea			***Dyspnea (Gr 3)***
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
SURGICAL AND MEDICAL PROCEDURES			
	Surgical and medical procedures - Other (packed RBC transfusion)		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS

SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

Also reported on MS-275 (SNDX-275, entinostat) trials but with the relationship to MS-275 (SNDX-275, entinostat) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Chest pain - cardiac; Conduction disorder; Heart failure; Left ventricular systolic dysfunction; Palpitations; Pericardial effusion; Pericarditis; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Anal mucositis; Colitis; Dysphagia; Esophageal pain;

Esophagitis; Gastrointestinal disorders - Other (hyperdefecation); Gastrointestinal hemorrhage[3]; Hemorrhoids; Mucositis oral; Pancreatitis; Periodontal disease; Rectal mucositis; Rectal pain; Small intestinal mucositis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Chills; Edema face; Injection site reaction; Multi-organ failure; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Activated partial thromboplastin time prolonged; CPK increased; GGT increased; INR increased; Investigations - Other (coagulopathy); Investigations - Other (vitamin D deficiency); Lipase increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoglycemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (thorax pain); Myositis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dizziness; Dysphasia; Intracranial hemorrhage; Neuralgia; Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Libido decreased
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary

disorders - Other (bladder distension); Renal hemorrhage; Urinary frequency; Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Atelectasis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pulmonary edema; Respiratory failure; Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Photosensitivity; Pruritus; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hyperkeratotic lesions/squamous cell carcinoma); Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event; Visceral arterial ischemia

Note: MS-275 (SNDX-275, entinostat) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List(s) for Irinotecan, Docetaxel, Pemetrexed, or Gemcitabine

Below are reported common side effects from these commercial agents. For additional side effects and information, please refer to package insert for individual agents.

Irinotecan

Cardiovascular: Vasodilation (9% to 11%)
Central nervous system: Cholinergic toxicity (47% - includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever (44% to 45%), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)
Dermatologic: Alopecia (46% to 72%), rash (13% to 14%)
Endocrine & metabolic: Dehydration (15%)
Gastrointestinal: Diarrhea, late (83% to 88%; grade 3/4: 14% to 31%), diarrhea, early (43% to 51%; grade 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), weight loss (30%), flatulence (12%), stomatitis (12%)
Hematologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%)
Hepatic: Bilirubin increased (84%), alkaline phosphatase increased (13%)
Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)
Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%)
Miscellaneous: Diaphoresis (16%), infection (14%)

Docetaxel

Cardiovascular: Fluid retention (13% to 60%; dose dependent)
Central nervous system: Neurosensory events (20% to 58%; including neuropathy),

fever (31% to 35%), neuromotor events (16%)
Dermatologic: Alopecia (56% to 76%), cutaneous events (20% to 48%), nail disorder (11% to 41%)
Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
Hematologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir (median): 7 days, duration (severe neutropenia): 7 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 94%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (6% to 12%; dose dependent)
Hepatic: Transaminases increased (4% to 19%)
Neuromuscular & skeletal: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%)

Respiratory: Pulmonary events (41%)
Miscellaneous: Infection (1% to 34%; dose dependent), hypersensitivity (1% to 21%; with premedication 15%)

Gemcitabine

Cardiovascular: Peripheral edema (20%), edema (13%)
Central nervous system: Fever (38% to 41%), somnolence (11%)
Dermatologic: Rash (28% to 30%), alopecia (15% to 16%), pruritus (13%)
Gastrointestinal: Nausea/vomiting (69% to 71%; grade 3: 10% to 13%; grade 4: 1% to 2%), diarrhea (19% to 30%), stomatitis (10% to 11%)
Hematologic: Anemia (68% to 73%; grade 4: 1% to 2%), leukopenia (62% to 64%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 36%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3: ≤2%; grade 4: <1%); myelosuppression is the dose-limiting toxicity
Hepatic: AST increased (67% to 78%; grade 3: 6% to 12%; grade 4: 2% to 5%), alkaline phosphatase increased (55% to 77%; grade 3: 7% to 16%; grade 4: 2% to 4%), ALT increased (68% to 72%; grade 3: 8% to 10%; grade 4: 1% to 2%), bilirubin increased (13% to 26%; grade 3: 2% to 6%; grade 4: ≤2%)
Renal: Proteinuria (32% to 45%; grades 3/4: <1%), hematuria (23% to 35%; grades 3/4: <1%), BUN increased (15% to 16%)
Respiratory: Dyspnea (10% to 23%)
Miscellaneous: Flu-like syndrome (19%), infection (10% to 16%; grade 3: 1% to 2%; grade 4: <1%)

Pemetrexed

Central nervous system: Fatigue (25% to 34%; dose-limiting)
Dermatologic: Rash/desquamation (10% to 14%)
Gastrointestinal: Nausea (19% to 31%), anorexia (19% to 22%), vomiting (9% to 16%), stomatitis (7% to 15%), diarrhea (5% to 13%)
Hematologic: Anemia (15% to 19%; grades 3/4: 3% to 4%), leukopenia (6% to 12%; grades 3/4: 2% to 4%), neutropenia (6% to 11%; grades 3/4: 3% to 5%; dose-limiting; nadir: 8-10 days; recovery: 4-8 days after nadir)
Respiratory: Pharyngitis (15%)

7.2 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. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through AdEERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

7.3.2 AdEERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. AdEERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Table 6: Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

- For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, AdEERS). The following AEs must be reported through the routine reporting mechanism (Section 7.4):

Table 7.

AE	Grade	Grade	Hospitalization/Prolongation of Hospitalization	Comments
Hemoglobin	3	4	**X**	Anemia
Leukocytes (total WBC)	3	4	**X**	Leukopenia
Neutrophils/granulocytes	3	4		Neutropenia
Platelets	3	4	**X**	Thrombocytopenia
Transfusion pRBC	3		**X**	

Fatigue (lethargy, maliaise, asthenia)	3		**X**	
Nausea	3		**X**	
Vomiting	3		**X**	
Diarrhea	3		**X**	
Infection with grade 3 or 4 neutropenia	3		**X**	
Infection without neutropenia	3		**X**	
Infection with unknown ANC	3		**X**	
Febrile neutropenia	3		**X**	

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through AdEERS must <u>also</u> be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 5-Azacitidine (NSC 102816)

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

8.1.1.2 **How supplied and preparation:** Azacitidine will be supplied by Celgene and distributed by Cancer Therapy Evaluation Program of the Division of Cancer Treatment and Diagnosis in the National Cancer Institute. 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. 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.

8.1.1.3 **Storage and Stability**: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration. Azacitidine is supplied as a lyophilized powder in 100 mg single-use vials. Store unreconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F).

8.1.1.4 **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.

8.1.1.5 **Administration:** To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. Azacitidine suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

8.1.1.6 **Toxicities:** In clinical studies, the most commonly occurring adverse reactions were nausea (70.5%), anemia (69.5%), thrombocytopenia

(65.5%), vomiting (54.1%), pyrexia (51.8%), leukopenia (48.2%), diarrhea (36.4%), fatigue (35.9%), injection site erythema (35.0%), constipation (33.6%), neutropenia (32.3%) and ecchymosis (30.5%). Other adverse reactions included dizziness (18.6%), chest pain (16.4%), febrile neutropenia (16.4%), myalgia (15.9%), injection site reaction (13.6%), aggravated fatigue (12.7%) and malaise (10.9%).

8.1.2 **CC-486 (NSC 102816)**

8.1.2.1 **Chemical Name:** 4-amino-1-[(2R,3R,4S,5R)-3,4-dihydroxy-5 (hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2-one
Other Names: 5-azacitidine, 5-aza, azacitidine, Vidaza®

8.1.2.2 **Classification:** antimetabolite, DNA hypomethylating agent

8.1.2.4 **CAS Registry Number:** 320-67-2
Molecular Formula: $C_8H_{12}N_4O_5$ **M.W.:** 244.2
Approximate Solubility: 89 g/L at 25° C in water

8.1.2.5 **Mode of Action:** Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is incorporated into DNA and RNA at high doses and causes direct cytotoxicity as a result of inhibiting DNA and RNA functions. It also inhibits DNA methyltransferase at low doses, therefore causing DNA hypomethylation and subsequent alterations in gene expression.

8.1.2.6 **How Supplied:** Celgene supplies and DCTC, NCI distributes oral azacitidine as 100 mg tablets, packaged in 21-count blisterpacks. Each film-coated tablet contains the following excipients: mannitol, silicified microcrystalline cellulose, crospovidone, magnesium stearate and hydroxypropyl cellulose.

8.1.2.7 **Storage:** Store less than 25° C.
Stability: Shelf life studies are ongoing.

8.1.2.8 **Route of Administration:** Take by mouth with 8 ounces of room temperature water on an empty stomach or with a light meal.

8.1.2.9 **Potential Drug Interactions***:* Azacitidine is neither metabolized by CYP450 isoenzymes nor an inhibitor or inducer of any CYP enzymes. The data suggest that it will not produce clinically-relevant drug-drug interactions. It is also not a substrate for P-glycoprotein and has no inhibitory effect on this transport system.

8.1.2.10 **Special Handling:** Per the manufacturer's instruction, do not use any tablets that are broken or damaged. Dispose of them using proper procedures for disposal of cytotoxic drugs.

8.1.2.11 **Patient Care Implications:** In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdosage.

8.1.3 **Entinostat (NSC 706995)**

8.1.3.1 **Chemical name:** 3-Pyridylmethyl N-{4-[(2-aminophenyl)carbamoyl]benzyl}carbamate
Other names: MS-27-275, MS-275, SNDX-275
Molecular Formula: $C_{21}H_{20}N_4O_3$ M.W.: 376.41
Classification: Antineoplastic; entinostat is an inhibitor of histone deacetylase

8.1.3.2 **How Supplied:** Entinostat is supplied by the Syndax Pharmaceuticals, Inc. and distributed by DCTD, NCI as 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 pigments (red and yellow) as colorants.

8.1.3.3 **Mechanism of Action:** Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin 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.

8.1.3.4 **Route of Administration:** Oral. Entinostat should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. Entinostat tablets should not be split, crushed, or chewed.

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

8.1.3.6 **Potential Drug Interactions:** Metabolism: Data from in vitro metabolism experiments demonstrated that entinostat is not metabolized by CYP enzymes (Acharya 2006), but UGT 1A4 did metabolize entinostat to its M2 glucuronide metabolite. No metabolites could be detected after incubation of entinostat in human liver micrsomes (Acharya 2006). While inhibition of CYP enzymes 2B6 and 3A4 was seen, the data show that the degree of inhibition makes it unlikely that any in vivo systemic interactions would occur. Intestional CYP3A4 may be inhibited by entinostat. However, entinostat did not inhibit any UGT enzymes tested. Entinostat was found to induce CYP 1A2, CYP 2C6, and CYP 2B8 as well as UGT 1A4. Finally entinostat was found to be a substate for P-gp and BCRP transporters, but did not inhibit either of these transport proteins.

8.1.3.7 **Toxicities:** In the Phase I clinical trial of entinostat in patients with hematologic malignancies frequent toxicities included fatigue, anorexia, nausea, and electrolyte disturbances. Thrombocytopenia, leukopenia, granulocytopenia, abdominal pain, hypoalbumemia, hypophosphatemia, increased SGOT/SGPT, headache, fatigue (lethargy, malaise, asthenia), anorexia, nausea and vomiting.

8.1.3.8 **Patient Care Implications**: Entinostat may cause fatigue or

malaises; advise patient to exercise cause while driving a vehicle or operating machinery. Administation of entinostat is contraindicated in patients with a history of allergy to entinostat or other medicaitons that have a benzamide structure (eg tiapride, remoxipride, clebropride). Careful monitoring of patients for signs of infection or reactivation of past infections is recommended, as reactivation of infection has been reported in patients treated with entinostat, in some cases without evidence of neutropenia. The clinical significance of this finding and the potential association with entinostat is unknown. Entinostat must not be used during pregnancy or while breast feeding. Women and men participating in entinostat clinical studies must agree to use acceptable contraceptive methods, as indicated in the clinical study protocol, during treatment and for 3 months thereafter.

8.1.4 **Agent Ordering and Agent Accountability**

8.1.5 **NCI-**supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.6 **Agent Inventory Records –** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI

Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2 Commercial Agents

Irinotecan
Chemical Name: (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1Hpyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate
How Supplied: Supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride.
Mechanism of Action: Topoisomerase I inhibitor
Route of Administration: Intravenous
Storage and Stability: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial should remain in the carton until the time of use.

Please refer to FDA-approved package insert for additional information about irinotecan.

Gemcitabine
Chemical Name: 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer)
How Supplied: Supplied in a sterile form for intravenous use only. Vials of gemcitabine HCl contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder.
Mechanism of Action: Anti-metabolite nucleoside analog
Route of Administration: Intravenous
Storage and Stability: Store in glass vials, at 15 to 30°C.

Please refer to FDA-approved package insert for additional information about gemcitabine.

Docetaxel
Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-l,2α,4,7β,10β,13α-hexahydroxytax-ll-en-9-one 4-acetate 2-benzoate, trihydrate
How Supplied: Supplied as a sterile, non-pyrogenic, pale yellow to brownish-yellow solution and is available as multiple concentrations and vial configurations. Consult specific product labels for preparation instructions and excipient information.
Mechanism of Action: Binds microtubules irreversibly to inhibit mitotic cell division.
Route of Administration: Intravenous

Storage and Stability: Store the unopened vials between 2°-25°C. Retain in the original package to protect from bright light

Please refer to FDA-approved package insert for additional information about d

docetaxel.

Pemetrexed
Chemical Name: L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate
How Supplied: Supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials
Mechanism of Action: Folate analog antimetabolite
Route of Administration: Intravenous
Storage and Stability: Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Please refer to FDA-approved package insert for additional information about pemetrexed.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Laboratory Correlative Studies

9.1.1.1 Plasma

9.1.1.2 Plasma samples will be obtained prior to initiation of therapy, one and two months after initiation of therapy (all arms), after completion of epigenetic therapy (arms A and B) and at time of progression. Some of these timepoints may be overlapping. Samples obtained up to one week before or after the anticipated timepoints are acceptable.

9.1.1.3 Quantitative candidate promoter methylation analysis will performed on APC, HCAD, p16, RASSF1A, GATA4, Actin

9.1.1.4 For specific instructions on acquisition and handling of plasma samples please refer to APPENDIX C

9.1.1.5 Biopsies

9.1.1.6 Tumor tissue must be available from all patients prior to initiation of protocol therapy, either from original diagnostic biopsy, or biopsy performed prior to initiation of protocol therapy. If possible, patients randomized to receiving epigenetic therapy will be re-biopsied prior to starting chemotherapy. As many of the following studies will be performed as tissue availability allows:
A. Quantitative candidate promoter methylation analysis: APC, HCAD, p16,

RASSF1A, GATA4, Actin

B. Mutation and translocation analysis of known biologically relevant driver mutations in non-squamous NSCLC to include: EGFR, KRAS, EML4-ALK, BRAF, PIK3CA, and ERBB2 overexpression
C. Gene expression analysis using the Affymetrix gene expression array platform
D. Promoter methylation analysis using the Illumina platform
E. Ki67 by immunohistochemistry
F. Expression of DNMT1, EZH2, BMI1, and SUZ12

9.1.1.7 For specific instructions on acquisition and handling of fresh or frozen tissue samples please refer to **LAB MANUAL**

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks 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.

	Study Calendar for Arms A and B: Patients Randomized to Epigenetic Priming													
	Prestudy	**Epigenetic therapy**					**Chemotherapy**						Week 24 from start of epigenetic therapy	Off study
		4-week cycles					3-week cycles							
							Odd-numbered cycles			Even-numbered cycles				
		Week 1	Week 2	Week 3	Week 4	Week 8	Week 1	Week 2	Week 3	Week 1	Week 2	Week 3		
Azacitidine[a]		X	X	X[a]										
Entinostat[b]		X	X											
Chemotherapy[c]							X	X[d]		X	X[d]			
Informed Consent	X													
Demographics	X													
Medical history	X													
Concomitant Medications	X	X					X			X				
Physical Exam	X	X		X			X							
Vital signs	X	X		X			X			X				
Height	X													
Weight	X	X					X			X				
Performance Status	X	X					X			X				
CBC w/diff., plts.	X	X		X			X			X				
Serum chemistries[e]	X	X		X			X			X				
Adverse Event Evaluation	X	X					X			X				
Tumor Measurements	X				X[f]							X	X	
Radiologic Evaluation	X				X[f]							X	X	
B-HCG[g]	X						X							
EKG	X													
Plasma	X				X[h]									X

Collection														
Tumor Biopsy	X					X[i]								

[a] ArmA: Azacitidine 40mg/ m^2 SC days 1-6 and 8-10
Arm B: CC-486 200 mg PO days 1-21

[b] Entinostat 7 mg PO days 3 and 10
NOTE: Epigenetic therapy is for 2 cycles only, except in patients with objective response

[c] Chemotherapy regimens include:
Docetaxel: 75mg/m^2 IV Day 1 of a 21 day cycle OR
Gemcitabine: 1000 mg/ m^2 IV Days 1 and 8 of a 21 day cycle OR
Irinotecan: 300mg/ m^2 IV Day 1 of a 21 day cycle OR
Pemetrexed: 500 mg/ m^2 IV Day 1 of a 21 day cycle
NOTE: Treatment on all chemotherapy regimens can continue until disease progression or other criteria as listed in section 5.5. Patients with stable disease after 2 cycles of chemotherapy return to epigenetic therapy for 2 additional cycles. See section 5.1 for details.

[d] Gemcitabine only

[e] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium

[f] Week 8 only

[g] Serum pregnancy test (women of childbearing potential)

[h] Weeks 4 and 8

[i] Optional, in week 8 biopsy only for patients with fresh baseline biopsy and consenting to re-biopsy (can be performed week 9 pre-treatment)

Study Calendar for Arm C: Patients Randomized to Chemotherapy Alone						
	Prestudy	3-week cycles			Week 24 from start of therapy	Off study
		Week 1	Week 2	Week 3		
Chemotherapy[a]		X	X[b]			
Informed Consent	X					
Demographics	X					
Medical history	X					
Concomitant Medications	X	X				
Physical Exam	X	X				
Vital signs	X	X				
Height	X					
Weight	X	X				
Performance Status	X	X				
CBC w/diff., plts.	X	X				
Serum chemistries[c]	X	X				
Adverse Event Evaluation		X				
Tumor Measurements	X			X[e]	X	
Radiologic Evaluation	X			X[e]	X	
B-HCG[d]	X					
Plasma Collection	X[f]	X[f]	X[f]			X[f]
Tumor Biopsy	X					

[a] Chemotherapy regimens include:
Docetaxel: 75mg/m^2 IV Day 1 of a 21 day cycle OR
Gemcitabine: 1000 mg/ m^2 IV Days 1 and 8 of a 21 day cycle OR
Irinotecan: 300mg/ m^2 IV Day 1 of a 21 day cycle OR
Pemetrexed: 500 mg/ m^2 IV Day 1 of a 21 day cycle

NOTE: Treatment on all regimens can continue until disease progression or other criteria as listed in section 5.5

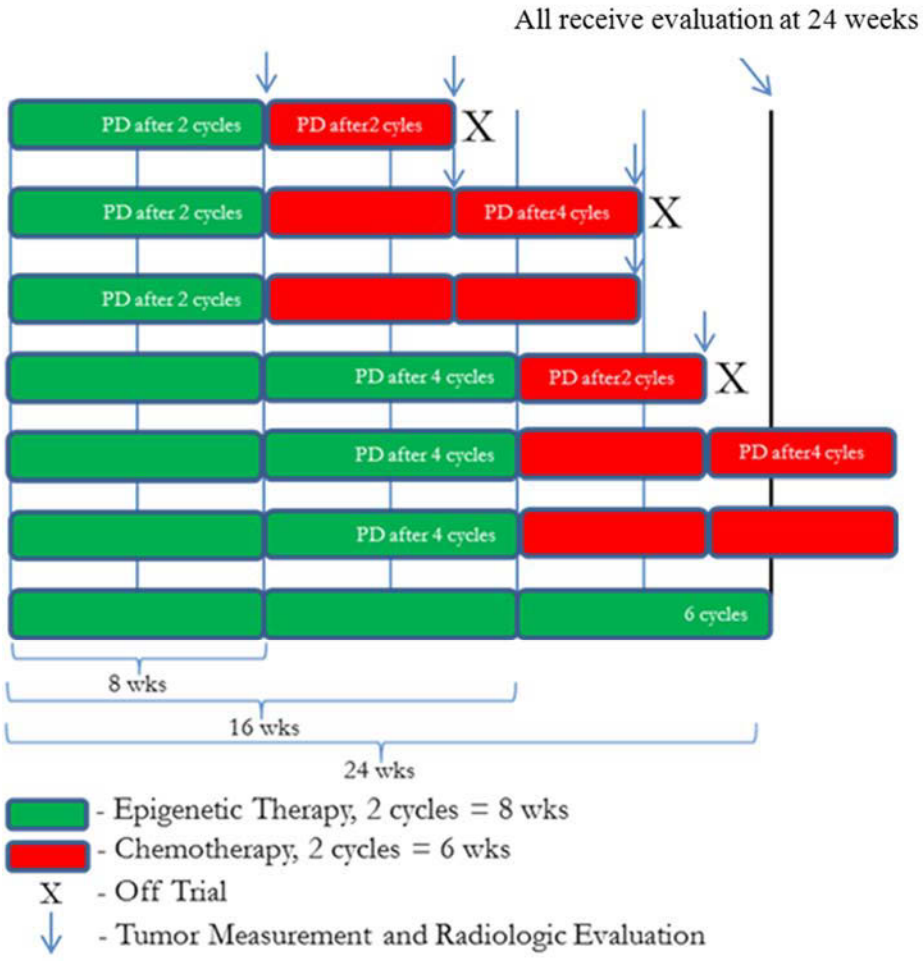
[b] Gemcitabine only

[c] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium

[d] Serum pregnancy test (women of childbearing potential)

[e] Week 3 of even numbered cycles only

[f] Plasma collection pretreatment, week 4 from start of therapy, week 8 from start of therapy, and off study, +/- 7 days for all time points. (time points for week 4 and week 8 do not necessarily correspond to a treatment day)



Tumor Measurement and Radiologic Evaluation Schema for Epigenetic Therapy Arm. The guiding principal is that every patient on study, regardless of arm, receives tumor reevaluation every two cycles, regardless of therapy.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

The primary endpoint of this study will be based on comparison of the baseline tumor assessment, performed prior to randomization to study arm, and assessment 24 weeks after randomization, using the RECIST 1.1 criteria described below. Scans performed up to 1 week prior to or after the planned time-points are acceptable. Additional scans, performed as defined in the study calendar, and will be used to assess objective response to individual components of

the therapy administered on this study, as well as progression-free survival, but will not be considered in assessment of the primary endpoint.

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 largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with azacitidine and entinostat.

Evaluable for objective response. 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 cycle 1 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.

11.1.2 Disease Parameters

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 might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same 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.

11.1.3 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 RECIST 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 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 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 need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. 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.
c. 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. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. 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.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 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. All patients on this study must have measurable disease.

Table 8. For Patients with Measurable Disease (*i.e.*, Target Disease)

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.

Table 9. For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 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.

11.1.6 Progression-Free Survival

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

11.1.7 Response Review

Baseline and 6 month scans of all patients will be reviewed by an attending radiologist to assign a response category.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

For phase 2 protocols: This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-

supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own

Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). -Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Study Design

The study will be a randomized phase II trial of single-agent chemotherapy alone or single-agent chemotherapy preceded by epigenetic therapy consisting of entinostat combined with either oral or subcutaneous azacitidine until progression is noted. Chemotherapy may be chosen from among irinotecan, docetaxel, gemcitabine, or pemetrexed by the treating physician. Patients will be stratified and randomized according to chemotherapy chosen.

13.1.2 Arms/Regimens

Patients will be randomized evenly to receive chemotherapy alone, chemotherapy primed by epigenetic therapy consisting of azacitidine 40 mg/m2/day subcutaneous days 1-6 and 8-10 and entinostat 7 mg PO days 3 and 10 on a 28 day cycle, or chemotherapy primed by epigenetic therapy consisting of CC-486 300 mg PO days 1-21 and entinostat 7 mg PO days 3 and 10 on a 28 day cycle until disease progression.

Chemotherapy will consist of one of the four following regimens chosen prior to randomization by the treating physician.

- Irinotecan 300mg/m^2 IV once every 3 weeks
- Docetaxel 75mg/m^2 IV once every 3 weeks
- Gemcitabine 1000g/m^2 IV days 1 and 8 of a 21 day cycle
- Pemetrexed 500 mg/m^2 IV once every 3 weeks (for non-squamous histology only)

13.1.3 Endpoints

13.1.3.1 Primary Endpoint

1) Percentage of patients progression-free at 6 months from the time of randomization.

13.1.3.2 Secondary Endpoint

1) Progression-Free Survival
   Progression-free survival (PFS) will be measured from the time of randomization until radiologic or clinical progression is noted.
2) Overall Survival
   Overall Survival (OS) will be measured from the time of enrollment to trial until death.

13.2 Sample Size/Accrual Rate

The study will enroll up to 165 patients, 55 per treatment arm. We will separately compare each treatment arm with epigenetic therapy (Arms A and B) to the single-agent chemotherapy arm (Arm C). The final analysis will be by Fisher's Exact test, with percentage of patients who have no progressed as the outcome variable. Using

Fisher's Exact test for analysis with 55 patients per treatment group will provide 88% power to detect an increase from 40% (chemotherapy alone) to 65% (epigenetic therapy followed by chemotherapy) in the number of patients who are progression free at six months. The power estimate is based on 1000 simulations of the 3-arm study with a one-sided 0.1-level of significance (see table below). We will not adjust for multiple comparisons, because the simulations of the three-arm study with futility monitoring (see Section 13.4) show that the Type I error is below 0.1. Allowing for up to 10% in-evaluable patients, we will enroll up to 61 patients per arm, or a total of 183. Anticipated accrual rate is 5 patients per month.

13.3 Stratification Factors

Treating physician will choose the chemotherapy for each subject. Patients will then be randomized to one of three arms, stratified by chosen chemotherapy.

13.4 Interim Analyses

The study design calls for separate interim futility analyses for each comparison of the chemotherapy alone arm to one of the arms with chemotherapy and epigenetic therapy. For each treatment pair, there will be two interim futility analyses. These analyses will occur after 20 patients and 40 patients per treatment group have been followed for 6 months. The futility analysis will project the final test based on current and predicted PD information. The Bayesian predictions are based on a Uniform(0,1) reference prior. We will consider closing a treatment arm with epigenetic therapy for futility if either interim analysis suggests that the predictive probability is 5% or less that there will ultimately be a significant difference between it and the single-agent chemotherapy arm. We estimated via simulation the study's operating characteristics (e.g., sample size, expected sample size, and error probabilities) considering these futility analyses. The following table displays the operating characteristics of the design and is based on 1000 simulations for each scenario.

Response Probability			Expected Sample Size			Probability Stop Trt A at Interim Analysis		Probability Stop Trt B at Interim Analysis		Probability Reject	
Control	**A**	**B**	**Control**	**A**	**B**	**#1**	**#2**	**#1**	**#2**	**A**	**B**
0.40	0.40	0.40	43.6	38.4	37.8	33.0%	33.7%	34.4%	34.6%	7.8%	8.0%
0.40	0.40	0.45	46.2	38.3	42.7	33.0%	34.4%	23.3%	27.4%	8.4%	17.6%
0.40	0.40	0.50	48.5	38.1	46.5	34.1%	32.8%	15.8%	19.5%	7.0%	31.1%
0.40	0.40	0.55	51.2	38.3	50.8	32.9%	34.3%	7.2%	11.5%	6.5%	53.9%
0.40	0.40	0.60	52.7	37.9	52.4	34.1%	34.6%	4.7%	6.3%	6.3%	74.0%
0.40	0.40	0.65	53.9	38.3	53.7	34.1%	32.0%	3.0%	1.6%	8.6%	88.1%
0.40	0.40	0.70	54.7	38.2	54.7	33.4%	34.2%	0.8%	0.4%	7.0%	95.9%
0.40	0.45	0.45	47.8	42.7	42.9	23.3%	27.8%	22.8%	27.4%	17.1%	18.4%
0.40	0.45	0.50	50.2	43.1	47.8	23.6%	24.0%	13.6%	16.2%	18.0%	36.1%
0.40	0.45	0.55	51.9	42.7	50.8	23.9%	26.2%	7.6%	10.3%	18.2%	54.5%
0.40	0.45	0.60	53.4	42.7	52.9	23.0%	28.6%	3.6%	5.7%	15.9%	75.1%
0.40	0.45	0.65	54.4	42.7	54.3	22.8%	28.5%	1.3%	1.8%	15.7%	88.9%
0.40	0.45	0.70	54.8	43.5	54.7	20.9%	28.2%	0.4%	1.0%	16.4%	96.9%
0.40	0.50	0.50	51.0	46.8	46.6	15.1%	19.5%	15.5%	19.8%	34.2%	35.8%
0.40	0.50	0.55	52.7	47.2	51.0	14.2%	18.9%	6.7%	11.3%	34.5%	54.4%
0.40	0.50	0.60	53.5	47.6	52.3	13.2%	18.7%	4.6%	7.0%	32.7%	72.2%
0.40	0.50	0.65	54.3	46.6	54.0	16.4%	17.5%	1.7%	2.5%	36.2%	87.7%
0.40	0.50	0.70	54.8	47.3	54.7	13.7%	19.5%	0.6%	0.4%	34.5%	95.5%
0.40	0.55	0.55	53.3	50.2	50.4	9.0%	10.9%	8.2%	11.2%	53.4%	54.4%
0.40	0.55	0.60	53.9	50.6	52.7	8.6%	9.6%	4.4%	5.3%	55.1%	74.5%
0.40	0.55	0.65	54.5	51.3	54.3	7.3%	7.9%	1.4%	1.5%	55.3%	90.3%
0.40	0.55	0.70	54.8	50.6	54.7	8.4%	9.6%	0.7%	0.6%	55.5%	95.8%
0.40	0.60	0.60	54.4	53.1	52.9	3.4%	4.6%	4.0%	4.8%	74.7%	74.7%
0.40	0.60	0.65	54.7	52.5	54.0	5.0%	4.7%	2.4%	1.4%	74.1%	87.9%
0.40	0.60	0.70	54.7	52.0	54.3	5.7%	6.5%	1.7%	0.4%	72.2%	95.2%
0.40	0.65	0.65	54.8	53.9	53.9	2.4%	2.0%	2.2%	2.4%	88.4%	88.9%
0.40	0.65	0.70	55.0	54.3	54.8	1.4%	1.4%	0.3%	0.6%	88.5%	97.1%
0.40	0.70	0.70	54.9	54.7	54.7	0.7%	0.4%	0.7%	0.2%	96.6%	96.2%

13.5 Analysis of Secondary Endpoints

While the trial is specifically powered for clinical endpoints we will report the outcome of laboratory studies performed on trial patient samples. Each of the proposed laboratory correlates will be performed for each patient, to the extent possible. Laboratory data will be used to identify patients likely to benefit from combination therapy and to refine therapy for future trials. Because multiple endpoints will be employed in correlate analysis, these will be used to generate hypotheses to be further tested in future studies.

i. The predictive and prognostic value of the previously defined epigenetic signature, comprised of promoter methylation analysis of 4 target genes, will be assessed
ii. Response to therapy compared to genetic and epigenetic factors and tested for association
iii. Genome-wide techniques will include expression array and methylation array will be compared to response.

13.6 Reporting and Exclusions

13.6.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with any study therapy.

13.6.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning

treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all

IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C: PLASMA AND SERUM PROCESSING PROTOCOL

Reagents:

- Ficoll-Paque Plus Buffer (must be stored at 4 degrees C)

Equipment:

- 15 mL conical tubes (1 for each tube of blood)
- 1.5 mL Eppendorf Tubes
- Plastic non-graduated disposable pipetters

Procedure:

Preparation-

1. First get the blood tubes (plasma and serum)
2. Get 1- 15mL conical per tube of serum or plasma.
3. Label each 15 mL conical with either plasma or serum, and the identification. This is only to be able to tell the samples apart if you are processing more than 1 patient at once
4. Take the labeled conicals marked plasma, and fill each one with 3 to 4 mL Ficoll- Paque buffer.
5. Take the plasma sample tubes (purple tops) and empty each one into the conicals containing the buffer. Pour very slowly as not to lyse the cells.

*** The plasma samples will have buffer in them, the serum ones will not

Spinning samples-

6. Take all of the plasma and serum 15 mL conicals and spin them a refrigerated centrifuge set at 4 degrees C. Spin at a speed of 3000 rpm for 10 min.
7. While the plasma and serum samples are spinning, set up and label your 1.5 mL Eppendorf tubes. You can start by labeling 4 tubes for serum and 4 for plasma. You might need more or less.
8. Each tube should have the random number and sample type on the top (serum = S, plasma = P). The side of the tube should have the random number, sample type, and date.
9. After the 10 min spin, take the plasma conicals out of the centrifuge and **spin the serum conicals for another 10 minutes.**
10. Get 1 disposable transfer pipette per sample type. Put the pipettes in the hood before you start opening the conicals.
11. Use the pipetter to carefully extract the plasma from the first conical, and transfer it into the pre-marked 1.5 mL Eppendorf tubes. Make sure you only take the yellowish fluid (the actual plasma). If you accidentally touch the red blood cells, don't take the rest of the sample from that tube. **If the plasma appears to be pink or red when you get it from the centrifuge, the cells have lysed. Take some of the sample, but note that the sample lysed.

12. After harvesting the plasma, set conical aside for 1 min. After 1 minute, collect the white, buffy coat layer into its own eppendorf tube using a transfer pipetter.

Storage:

13. Once all of the samples have been taken, note what samples you have and record the necessary information in a spreadsheet or database. (ex. How many vials are collected, blood processing times, etc.)
14. Snap freeze all samples at -80 degrees Celsius.

APPENDIX D: PATIENT DIARY FOR ARM A PATIENTS

Patient initials_____ Cycle_____ MRN_____

Please take your anti-nausea medicine and entinostat 7 mg by mouth on days 3 and days 10 of each 28 day cycle. **Do not start cycle 2 until after 28 days.**
*** Entinostat should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. If your dose requires more than one tablet, the tablets should be taken one at a time.
***Your anti-nausea medicine should be taken at least 30 minutes prior to entinostat.

Day/Date	**entinostat** *Check box and note time taken below*: ***Please note time next to the box.*** **AM** **OR** **PM**		**Comments: Please note any side-effects you may be having or problems with compliance.**
Cycle 1			
Day 3			
Day 10			
Cycle 2			
Day 3			
Day 10			

APPENDIX E: PATIENT DIARY FOR ARM B PATIENTS

Patient initials_____ Cycle_____ MRN_____

Please take CC-486 (oral azacitidine) 300 mg by mouth once daily, Days 1 through 21 of each 28-day cycle. **Do not start cycle 2 until after 28 days.**
***You should drink 8 ounces (240 mL) of room temperature water with each dose. Oral azacitidine may be taken on an empty stomach or with food.

Please also take entinostat 7 mg PO (by mouth) on days 3 and days 10 of each 28 day of cycle 1 and cycle 2. **Do not start cycle 2 until after 28 days.**
*** Entinostat should be taken on an empty stomach. If your dose requires more than one tablet, the tablets should be taken one at a time.
***Your anti-nausea medicine should be taken at least 30 minutes prior to entinostat.

Day/Date	**CC-486 (oral azacitidine)** *Check box and note time taken below*: ***Please note time next to the box.*** **AM OR PM**		**Entinostat** *Check box and note time taken below*: ***Please note time next to the box.*** **AM OR PM**		**Comments: Please note any side-effects you may be having or problems with compliance.**
Cycle 1					
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8					
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15					
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					

Day 21				
(wait until after Day 28 to start cycle 2)				
Day/Date	**CC-486 (oral azacitidine)** *Check box and note time taken below*: ***Please note time next to the box.*** **AM OR PM**		**Entinostat** *Check box and note time taken below*: ***Please note time next to the box.*** **AM OR PM**	**Comments: Please note any side-effects you may be having or problems with compliance.**
Cycle 2				
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				