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SUMMARY OF CHANGES

For Protocol Amendment #1:

NCI Protocol #: NRG-GY011
Local Protocol #: NRG-GY011

NCI Version Date: 11/20/2018
Protocol Date: 11/20/2018

This amendment is being submitted in response to an RA from Dr. Richard Piekarz (piekarzr@mail.nci.gov)

#	Section	Page(s)	Comments
1	Title Page	**1-2**	**NCI Version Date has been updated throughout the protocol.** **Document History has been updated**
	7.2		**The CAEPR for entinostat has been replaced per request for amendment from NCI.**

NRG-GY011
(ClinicalTrials.gov NCT #TBD)

A Randomized Surgical Window Pilot Investigation of the Relationship of Short Term Medroxyprogesterone Acetate (NSC #26386) Compared to Medroxyprogesterone Acetate Plus Entinostat (NSC #706995) on the Morphologic, Biochemical, and Molecular Changes in Primary Endometrioid Adenocarcinoma of the Uterine Corpus

NCI Version Date: 11-20-18

This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.
Lead Organization: NRG / NRG Oncology

Participating Organizations
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

Coordinating Center:
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Protocol Agent

NCI-Supplied Agent(s): Entinostat, NSC 706995

Other Agent(s): Medroxyprogesterone Acetate, NSC 26386, Commercial

IND Sponsor: DCTD, NCI

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Closure		
Amendment 2		

Update		
Amendment 1	November 20, 2018	
Update		
Activation	August 1, 2017	August 25, 2017
Pre-Activation		

NRG-GY011

A Randomized Surgical Window Pilot Investigation of the Relationship of Short Term Medroxyprogesterone Acetate (NSC #26386) Compared to Medroxyprogesterone Acetate Plus Entinostat (NSC #706995) on the Morphologic, Biochemical, and Molecular Changes in Primary Endometrioid Adenocarcinoma of the Uterine Corpus

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via: **ONLINE**: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) **EMAIL**: CTSURegulatory@ctsu.coccg.org (regulatory documentation only) **FAX**: 215-569-0206 **MAIL**: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 For regulatory questions call the CTSU Regulatory Help Desk at 1-866-651-CTSU	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

TABLE OF CONTENTS

NRG-GY011
SCHEMA

DIAGNOSIS OF PRIMARY ENDOMETRIOID ADENOCARCINOMA OF THE UTERINE CORPUS BY D&C OR BIOPSY (FORMALIN-FIXED, PARAFFIN-EMBEDDED TUMOR TISSUE MUST BE SUBMITTED)

↓

PATIENT ENTRY

↓

MEDROXYPROGESTERONE ACETATE 400 MG IM, GIVEN ONCE, 21-24 DAYS PRIOR TO HYSTERECTOMY on day 1

Randomize

ENTINOSTAT 5 mg PO Days 1, 8 and 15	NO TREATMENT

↓

STANDARD SURGICAL THERAPY
(HYSTERECTOMY, BSO, +/- LYMPH NODE SAMPLING; FORMALIN-FIXED, PARAFFIN-EMBEDDED TUMOR TISSUE MUST BE SUBMITTED)

↓

OFF TREATMENT

30-45 day follow-up for safety

Safety assessment must occur prior to beginning any adjuvant therapy

Safety exam will coincide with post-operative visit

1. OBJECTIVES

1.1 Primary Objective

To determine whether the addition of the histone deacetylase inhibitor, entinostat, in combination with medroxyprogesterone acetate in the pre-operative setting results in up-regulation of activated progesterone receptors (PR) compared to medroxyprogesterone acetate alone.

1.2 Secondary Objectives

To assess the response rate (as measured by cellular morphology and proliferation) and change in activated receptor levels with the addition of entinostat at the time of hysterectomy.

2. BACKGROUND

2.1 Progesterone signaling through its receptor (PR) is the ultimate tumor suppressor of the endometrium.[19] However, long-term progestin treatment is associated with the down-regulation of PR; this down-regulation is hypothesized as the reason why hormonal therapy with progestin for endometrial cancer has limited long-term effectiveness.[20] The purpose of this trial is to demonstrate that PR remains upregulated and sensitive to progestin when the progesterone medroxyprogesterone acetate is given with the HDAC inhibitor entinostat, more than when compared with medroxyprogesterone acetate alone.

Endometrial cancer is a hormone-dependent malignancy, and hormone therapy has long been applied to treat endometrial cancer patients. Endometrial cancer patients treated with synthetic progesterone/progestin have achieved promising clinical outcomes; overall response rates are 50-70% for primary (mainly pre-menopausal) endometrial cancer patients[10] and 27-33% for advanced endometrial cancer patients.[4] The presence of PR on endometrial cancer cells has been shown to be strongly associated with response to progesterone treatment.[7] The overall response rate to progesterone treatment has been reported to be 72% in patients with PR-positive tumors but only 12% in patients with PR-negative lesions.[7] Additionally, in advanced and recurrent disease, a difference in response with respect to grade can be seen: in GOG-0081, the ORR was 37% in the patients whose cancer was PR positive (16/46) compared to 8% (7 of 86) in the patients whose cancer was PR negative.[17] Overall expression of progesterone receptor correlates with a good prognosis and response to progestin treatment. For clinical purposes (and in the studies mentioned), merely the presence or absence of IHC expression of PR is used to make decisions regarding appropriate use of hormonal therapy. The presence of PR is recorded as either positive or negative, with the actual quantity of PR expression unmeasured.

In GOG-0119, which considered patients with measurable, advanced or recurrent endometrial cancer, 45% of the lesions were demonstrated to be PR positive, and the level of PR expression decreased significantly with increasing tumor grade (see Table, below).[15] In GOG-0119, the immune-staining for ER and PR was semi-quantified using the HSCORE method.[11] In GOG-0119, a threshold of > 75 for ER as a positive result was chosen to provide the maximum sensitivity and specificity and as a benchmark for tumors

that responded to therapy.

Table 1: Adapted from GOG 119[15]

	Grade 1	Grade 2	Grade 3 or unspecified
PR negative	6	7	14
PR positive	6	9	7

GOG-0211 was the first non-therapeutic pre-operative window trial in women with endometrial cancer.[23] After diagnosis of endometrial cancer by endometrial biopsy, patients were enrolled to receive medroxyprogesterone acetate 21-24 days prior to planned surgery. The biopsy and hysterectomy specimens were evaluated for estrogen and progesterone receptor expression, as well as other markers for proliferation and apoptosis. As in GOG-0119, the receptor IHC was semi-quantified.

Fifty-nine women received treatment with progestin per protocol and had available slides. One complete histologic response was seen, and 37 tumors (64%) had a partial response. The low complete response rate seen in GOG-0211 might have been in part due to the older age of the women in the study, the (very) short duration of progesterone treatment, and the large percentage of women with grade 3 tumors (15%). Nevertheless, there were significant histologic changes seen in the majority of patients following treatment that suggest a higher rate of progesterone response than evidenced by complete regression of disease. Specific quantifiable, statistically significant histologic changes that occurred in the carcinomas following administration of progestin included: 1) a decrease in the number of mitotic figures; 2) a decrease in high nuclear grade; 3) acquisition of more abundant eosinophilic cytoplasm; 4) a decrease in mean gland cellularity; 5) a decrease in the frequency of nucleoli; 6) increased mucinous and/or squamous metaplasia; and 7) the presence of subnuclear, apical or intraluminal secretion. The tumors that displayed a partial or complete histologic response following treatment differed initially from those that did not respond in that the responders had a lower initial mitotic index and lower initial nuclear grade than the non-responders (with response defined with very specific pathologic parameters).[23]

The model used in GOG-0211 also allowed assessment of the tumor microenvironment: in the case of endometrial cancer, this includes the adjacent normal endometrium as well as the endometrial stroma. Decidual change (a histologic marker of stromal progesterone effect) was entirely confined to the stroma surrounding benign appearing glands in 12 of the 14 cases in GOG-0211. Interestingly, the decidual change was more likely to occur in the benign portions of endometrium adjacent to carcinomas that showed a histologic response.[23] This finding suggests a paracrine effect in which some gland:stromal interaction may be essential for either decidualization or complete tumor cell differentiation to occur. This mechanism may be critical to tumor response.

Most germane to the current study, GOG-0211 demonstrated a down-regulation of PR following progesterone treatment. A statistically significant decrease was identified in the

mean ER, PR, and PRB following 21 days of progestin treatment. The table below, adapted from GOG-0211, demonstrates the change in hormone receptor expression in the total population of patients as well as in responders and non-responders to progesterone treatment.

Table 2: Immunohistologic characteristics for ER, PRA, PRB, before and after medroxy-progesterone acetate. Adapted from GOG-0211.[23] The numbers shown in Table 3 represent modified H scores defined by the proportion of nuclei staining (0-1) X the intensity (1+-3+)

	Pretreatment		Posttreatment		Change		
	Mean	SE	Mean	SE	Mean	SE	*P*†
ER							
Total (n = 53)	2.07	0.11	1.30	0.12	−0.77	0.14	<0.001
Responder (n = 36)	1.99	0.14	1.31	0.15	−0.68	0.17	<0.001
Nonresponder (n = 17)	2.25	0.21	1.29	0.21	−0.96	0.22	<0.001
PR							
Total (n = 53)	1.78	0.14	0.66	0.11	−1.12	0.15	<0.001
Responder (n = 36)	1.87	0.17	0.79	0.14	−1.08	0.16	<0.001
Nonresponder (n = 17)	1.60	0.26	0.38	0.19	−1.22	0.34	0.002
PRB							
Total (n = 52)	1.36	0.15	0.43	0.11	−0.94	0.14	<0.001
Responder (n = 36)	1.52	0.18	0.52	0.15	−1.00	0.16	<0.001
Nonresponder (n = 16)	1.00	0.29	0.21	0.10	−0.80	0.25	0.006

2.2 Modulation of progesterone receptor expression

In hormonally responsive tissues, PR is activated by ligand, then binds to DNA and is thereafter rapidly removed from DNA by ubiquitination. This is followed by degradation in the proteasome. Rapid cycling on/off DNA enhances PR activity. Hence, short term PR depletion is a natural result of PR activity, and PR protein levels will wax and wane within a modest range as long as new PR molecules are replenished by *PgR* gene transcription. Yet, in many endometrial cancers, *PgR* is epigenetically silenced leading to long-term downregulation of PR and hormonal insensitivity. Persistent downregulation of PR removes one of the least toxic and most effective therapeutic opportunities for treatment of endometrioid endometrial cancer. The PR gene has been shown to be methylated in its promoter and exons, both in tumors from patients and in existing endometrial cancer cell lines, in response to progestational therapy.[13] It is postulated to be a major reversible mechanism of PR regulation and one that, as yet, has not been exploited therapeutically.

A principal goal of this trial is to determine the impact of progestin +/- entinostat on the activity of progesterone receptors (PR) in endometrial cancer. PR activity will be determined by the expression of an integrated biomarker, Ki67. Progestin binding activates PR as a differentiating transcription factor and results in inhibition of cellular proliferation, which can be assessed by observing a significant reduction in Ki67, and in

cell cycle arrest as determined by the significant induction of the cyclin dependent kinase p21. The expression of Ki67 (integrated) and p21 (exploratory) by immunohistochemistry on pre- versus post-treatment endometrial cancer samples reliably indicates both the activity of PR (p21 is a known gene that is highly induced by PR) and the inhibition of proliferation (reduced Ki67) resulting from hormonal therapy. PR levels per se are also somewhat informative and will be assessed by immunohistochemistry for PR, which is another integrated biomarker. However, levels of PR protein alone are not a completely reliable indication of PR activity because even active PR may be down-regulated in the short term as a result of the normal ligand-dependent PR shuttling to the proteasome. Hence, we propose that adding an integrated biomarker strongly indicative of PR activity and therapeutic effectiveness (Ki67) will allow a more complete understanding of the impact of treatment at the molecular level.

Histone deacetylation is an important epigenetic modulator. The two FDA-approved HDAC inhibitors vorinostat (SAHA) and depsipeptide (romidepsin) are intravenously administered HDAC inhibitors; several others are under development, including the orally administered entinostat. DNA methylation is another method of re-regulation. Two DNA methyltransferase (DNMT) inhibitors have been approved by the FDA, 5-azacytidine (Vidaza) and 5-aza-deoxycytidine (decitabine). These agents are administered IV. The oral agent was chosen for the current study as it is logistically less complicated in this setting.

There are many promising preclinical reports to encourage the study of epigenetic therapies for endometrial cancer.[21] Treatment with DNMT inhibitors restores expression of several genes that have been shown to be methylated in endometrial and ovarian tumors, including PR. For example, the DNMT inhibitor 5-azacytidine restored PR expression in KLE endometrial cancer cells, which are normally negative for PR.[14] Additionally, the HDAC inhibitor vorinostat (SAHA) inhibited growth of endometrial cancer cells in vitro and in vivo in xenograft models of endometrial cancer, with no toxicity.[16] The work from Dr. Leslie's laboratory (shown below) suggest that the combination of entinostat and progesterone upregulates and maintains PR levels and induces cellular differentiation.[21] Additionally, the concentrations achieved in vitro are clinically relevant and achievable.[1]

<u>Preliminary Data Supporting the Biologic Endpoints and Study Rationale</u>:

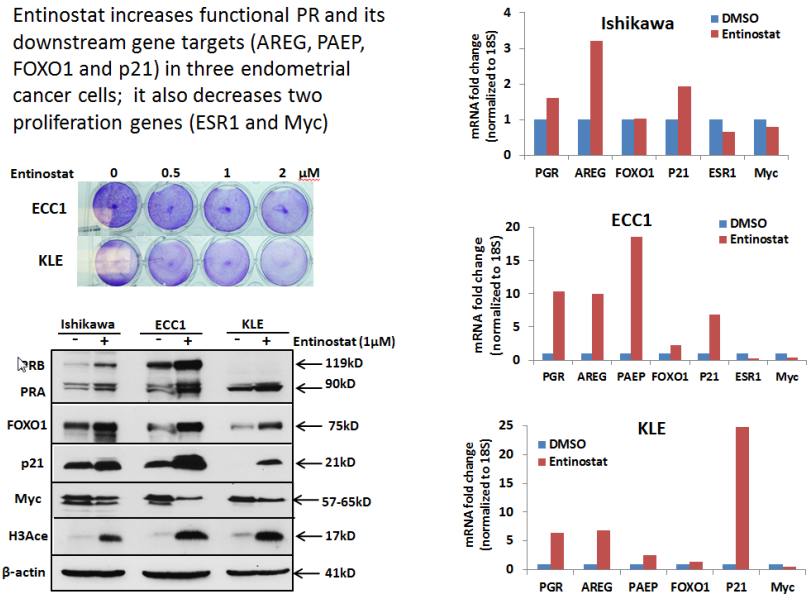

Figure 1. Multiple HDAC inhibitors have the capacity to induce functional PR expression. Functional expression of PR was examined in endometrial cancer cells in response to treatment with entinostat. The anticipated upregulation in PRA and B protein expression and progesterone-dependent downstream genes including FOXO1, AREG, and p21 was observed. Histone 3 acetylation was also induced as an effect of the drugs. Preliminary data provided by S. Yang and K. Leslie, the University of Iowa.

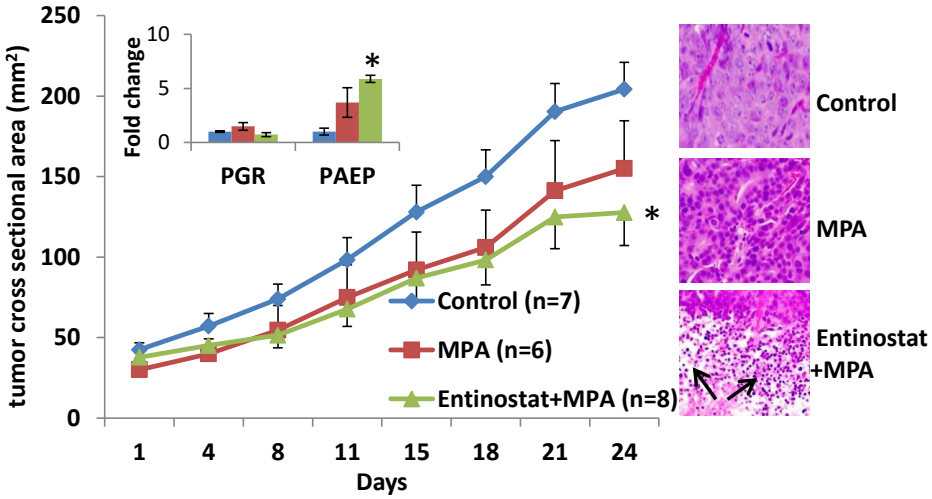

Figure 2. Molecularly enhanced progestin therapy with HDACi. Xenografts were created with Ishikawa cells and treated with MPA (1mg weekly i.m.) -/+ entinostat (15mg/kg, oral, daily). **Inset:** qRT-PCR analysis of PR and downstream gene PAEP at day 24. *Note: tumors from entinostat+MPA group (but not control or MPA alone) were primarily necrotic tissue (80%, shown with arrows), which may explain the low PR mRNA levels at day 24.* * $p<0.05$ vs. control. ***NOTE: Of the total tumor cross sectional area in the entinostat + MPA group, only 20% remained viable tumor, the rest was necrosis. Hence, the total area of the tumor under-estimated the therapeutic effect specifically with the combination regimen***. Preliminary data provided by S. Yang and K. Leslie, the University of Iowa.

2.3 Rationale for the combination of hormones and epigenetic therapies

Hormone therapy has shown promising clinical outcomes, but response is often short-lived, possibly partially due to down-regulation of PR, and endocrine agents are less likely to be effective in higher grade endometrial cancers, due to lower expression of PR in high grade cancers. We hypothesize that exposure to epigenetic therapy will sustain and potentially boost PR expression, and further study of this combination will result in improved response rate due to enhanced PR activity. We propose this randomized non-treatment trial to examine this novel and potentially therapeutic mechanism and to provide preliminary clinical data to lead into a randomized phase II study.

2.4 Feasibility and Rationale for the Neoadjuvant Model

The successful completion and publication of GOG-0211 suggests that a non-therapeutic surgical window study design can be performed in the Network Group. Other investigators have demonstrated the feasibility of complex surgical window trials with multiple translational endpoints in endometrial cancer patients. Dr. Duska has successfully completed a surgical window trial of dasatinib prior to hysterectomy for endometrial cancer; these results have been presented at SGO (2013, 2014)[5, 6] and are currently being prepared for publication. The study format was both acceptable to patients and safe. The MD Anderson group presented a similar concept study at ASCO 2014. These studies and others suggest these purely scientific studies are feasible and safe.

The effect of the combination of progesterone and entinostat on PR expression in endometrial cancer can best be studied via the neoadjuvant mechanism proposed above because there is no need for extra non-clinical biopsies to be performed, thus increasing patient acceptability and decreasing cost. The flexibility of using the diagnostic biopsy followed by ascertainment of the clinical material after a lead-in treatment phase makes this proposed process cost and time efficient with little or no downside to patients who are already planning surgery for their endometrioid endometrial cancer.

2.5 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not

permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Women of childbearing potential must be willing and able to use medically acceptable forms of non-hormonal contraception (barrier methods) during the trial and for 3 months after the use of entinostat (if surgery is not performed).

3.1.2 Submission of tumor tissue is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial.

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Patients must have a histologically proven diagnosis of endometrioid endometrial adenocarcinoma by endometrial curettage or biopsy within 8 weeks prior to registration. Central pathology review will be required as part of the study but not for registration purposes.

3.2.2 History/physical examination within 42 $\pm$ 5 days of planned surgical procedure (18-21 days from day 1Further protocol-specific assessments as detailed in the table in Section 4.

3.2.3 Age $\geq$ 18

3.2.4 The trial is open only to women with primary endometrioid adenocarcinoma of the uterine corpus (all histologic grades and stages) who are planned and appropriate for primary surgical treatment to include removal of the uterine corpus via any surgical modality. The patient must be considered a suitable surgical candidate.

3.2.5 Patients must have an ECOG Performance Status of 0, 1, 2, or 3 within 28 days prior to registration (See Appendix I)

3.2.6 Formalin-fixed, paraffin-embedded tumor tissue from the biopsy or curettage must be submitted along with the corresponding pathology report. (See Section 10.3 for details.)

3.2.7 Adequate hematologic function defined as follows:

- Platelets $\geq$ 100,000/µl
- Granulocytes (ANC) $\geq$ 1,500/µl

3.2.8 Adequate renal function defined as follows:

- Creatinine $\leq$ 1.6 mg/dl

3.2.9 Adequate hepatic function defined as follows:

- SGPT (ALT) $\leq$ 3 x upper limits of normal
- Bilirubin within institutional normal limits.

3.2.10 The patient must provide study-specific informed consent and authorization permitting release of personal health information prior to study entry.
3.2.11 Any patients of childbearing potential must have a negative pregnancy test.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Patients with any non-endometrioid histology (such as serous, clear cell, or carcinosarcoma).
3.3.2 Patients who have received prior progestin or anti-estrogen therapy during the 3 months before the diagnosis of endometrioid adenocarcinoma of the uterine corpus is established. Estrogen therapy alone is allowed.
3.3.3 Patients with ECOG Performance Grade of 4. (See Appendix I)
3.3.4 Patients with history of thrombophlebitis within the past 2 years or ongoing thromboembolic disorders.
3.3.5 Patients who have previously received systemic, radiation or other treatment for uterine cancer
3.3.6 Patients for whom formalin-fixed, paraffin-embedded tumor tissue from the biopsy or curettage is unavailable
3.3.7 Patients must not have previously received a non FDA approved HDAC inhibitor in a clinical trial setting (entinostat, belinostat.).
3.3.8 Patients must not be currently taking or have ever taken vorinostat (Zolinza, Merck), panobinostat (Farydak, Novartis) or romidepsin (Istodax, Gloucester Pharmaceuticals).

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

Procedure	Screening/Baseline (preop visit – within 42 days plus or minus 5 days of surgery	Day 1 (day of MPA treatment)	Day 8	Day 15	Day 15-18	Day 22-25	30-45 days post surgery
Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical History	X						
Physical Examination	X						X
Vital Signs (BP, Temp, Pulse, RR), ECOG PS	X						X
Height/Weight	X						
Randomization	3						
Concomitant Treatment Assessment	X						
Adverse Event Assessment		X	1	1	2	X	X
Laboratory Tests CBC, CMP	X				4		
Pregnancy Test (WOCBP)	X						
medroxyprogesterone		X					
Entinostat (Arm B Only)		X	X	X			

1. For Arm B, within 3 days of each entinostat administration, may be done by telephone
2. Within 7 days of surgery, may be done by telephone
3. May occur on day of screening or any time prior to day 1 (including day 1).
4. Only CBC needed, between 7 days pre-op and immediately pre-operatively

5. TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

5.1 When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

5.1.1 The institution must follow registration information in Section 8.

5.1.2 Request one bottle of entinostat 5 mg tablets, if the patient is randomized to the entinostat arm and the site does not have a bottle in stock.

5.2 Treatment Plan

5.2.1 Medroxyprogesterone acetate Administration in All Patients. Patients must be registered into study prior to administration of medroxyprogesterone acetate. All women will receive medroxyprogesterone acetate, 400 mg IM, given once 21-24 days prior to definitive surgical therapy. The date of medroxyprogesterone acetate injection will be designated as day 1.

5.2.2 Patients who are randomized to receive entinostat will be treated with entinostat 5 mg PO on day 1 (with medroxyprogesterone acetate injection). The remaining doses will be dispensed to the patient to be taken at home on days 8 and 15.

5.3 Standard Surgical Therapy for All Patients.

All women will receive standard surgical therapy (Hysterectomy, BSO, +/- lymph node sampling) 21-24 days following medroxyprogesterone acetate administration.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

The most commonly reported non-hematologic adverse events for entinostat are nausea, fatigue, and dry skin. The majority of these AE's are grade 1 or 2. It is suggested that anti-nausea medication be prescribed by the enrolling physician to be used at patient discretion. No other supportive medications are required for this study.

5.4.2 Prohibited Therapies: Patients must not have previously received an HDAC inhibitor in a clinical trial setting (entinostat, belinostat,). Patients must not be currently taking or have ever taken vorinostat (Zolinza, Merck) or panobinostat (Farydak, Novartis) or romidepsin (Istodax, Gloucester Pharmaceuticals).

5.5 Duration of Therapy

All patients will receive a single dose of medroxyprogesterone acetate followed by surgery 21-24 days later. Patients who receive a treatment assignment that includes entinostat are expected to complete all 3 doses of drug pre-operatively. Patients may stop entinostat for the following indications:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in 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. Follow up should continue however.

Patients who complete 2 doses will be allowed to stay on study and will be considered evaluable. Patients who complete 0 or 1 dose will still be followed per protocol (they will still be followed by their doctors and surgeons for consideration of surgery, and will still be followed for toxicity since they will have received the dose of medroxyprogesterone Acetate).

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 No dose escalations or reductions will be used.

6.2 All patients will have a second CBC drawn prior to surgery (may range from 7 days prior to day of surgery). A preoperative platelet value of less than 50,000/µl will delay surgery until resolution to greater than 50,000/µl.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

Entinostat is investigational agent administered on NRG-GY011, and is available under IND# TBD sponsored by DCTD, NCI. For patients receiving entinostat, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5.2.1 of the protocol.

Commercial Agents

Medroxyprogesterone acetate is commercial agent administered on NRG-GY011. For patients receiving medroxyprogesterone acetate, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5.2.2 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following lists of AEs (Sections 7.3 and 7.4) and the characteristics of an observed AE (Sections 7.2.2 and 7.2.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting

7.2.2 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

7.2.3 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not

considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Study Agents

7.3.1 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 221 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 2.5, September 10, 2018[1]

Adverse Events with Possible Relationship to MS-275 (SNDX-275, entinostat) (CTCAE 5.0 Term) [n= 221]			**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)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
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)***
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to MS-275 (SNDX-275, entinostat) (CTCAE 5.0 Term) [n= 221]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alkaline phosphatase increased		***Alkaline phosphatase 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)***
	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)***
	Hyponatremia		***Hyponatremia (Gr 3)***
Hypophosphatemia			***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
Headache			***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	

[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 INFESTATION 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.

Adverse events reported on MS-275 (SNDX-275, entinostat) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MS-275 (SNDX-275, entinostat) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac disorders - Other (transient right-side heart failure with worsening tricuspid regurgitation); 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; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastrointestinal disorders - Other (hyperdefecation); Gastrointestinal hemorrhage[3]; Hemorrhoids; Mucositis oral; Pancreatitis; Periodontal disease; Rectal mucositis; Rectal pain; Small intestinal mucositis; Typhlitis; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Generalized edema; Injection site reaction; Multi-organ failure; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Investigations - Other (coagulopathy); Investigations - Other (vitamin D deficiency); Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (thorax pain); Myositis; Pain in extremity
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; Seizure; 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 calculi; Renal hemorrhage; Urinary frequency; Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Atelectasis; Epistaxis; 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
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (packed RBC transfusion)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event

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.

7.4 Adverse Events for the Commercial Study Agent, Medroxyprogesterone Acetate

- breakthrough bleeding (premenopausal)
- spotting (premenopausal)
- change in menstrual flow (premenopausal)
- amenorrhea, headache
- nervousness

- dizziness
- edema
- change in weight (increase or decrease)
- changes in cervical erosion and cervical secretions
- cholestatic jaundice including neonatal jaundice
- breast tenderness and galactorrhea
- skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash
- acne, alopecia and hirsutism
- rash (allergic) with and without pruritis
- anaphylactoid reactions and anaphylaxis
- mental depression
- pyrexia
- fatigue
- insomnia
- nausea
- somnolence

Refer to the package insert for detailed pharmacologic and safety information and for a more comprehensive list of adverse events.

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP for this study by telephone at 301-897-7497 and to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 3 days.
- Supporting source documentation is requested by the IND Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. When

submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and to the NRG Regulatory Affairs at 215-854-0716.

- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events

7.5.2.1 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 electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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 submitted electronically 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 electronically 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

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 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 during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. 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.

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.

Other protocol-specific text to be added as needed

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Access requirements for OPEN and Medidata Rave: Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management

(IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures below for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

8.1.1 Investigator Registration Requirements

Prior to the recruitment of a patient for this study, investigators must be registered members of a Lead Protocol Organization. Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature;
- a current ***Curriculum Vitae*** (CV);
- a completed and signed ***Supplemental Investigator Data Form*** (IDF);
- a completed ***Financial Disclosure Form*** (FDF) with an original signature.

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

8.2 Site Registration Requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

8.2.1 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but

not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Protocol documents can be downloaded from the NRG Oncology website: www.nrgoncology.org

Requirements For NRG-GY011 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Checking Your Site's Registration Status:
You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-

IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.3 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- *If specific tests and/or bio-specimen is required before enrollment, add to bulleted list above.*

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: [email to come] or call the NRG Registration Desk at [phone number to come], Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the

registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

8.4 Agent Ordering and Agent Accountability

8.4.1 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.

8.4.2 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 Oral Drug Accountability Record Form (Oral DARF) available on the CTEP forms page. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.4.3 The current versions of the entinostat IB for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.4.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov

- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBCoordinator@mail.nih.gov

9. DRUG INFORMATION

9.1 Entinostat (NSC 706995)

9.1.1 **Other names:** MS-27-275, MS-275, SNDX-275

Classification: Histone deacetylase inhibitor (HDACi)

Molecular formula: $C_{21}H_{20}N_4O_3$ **M.W.:** 376.41

9.1.2 **Mode 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.

9.1.3 **How Supplied:** Entinostat is supplied by the Syndax Pharmaceuticals, Inc. and distributed by DCTD, NCI as 5 mg (yellow, in bottles of 5) 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.

9.1.4 **Storage:** Store the bottles at controlled room temperature (15-25ºC), and protect from light. Entinostat is not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC).

If a storage temperature excursion is identified, promptly return the entinostat to 25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 **Stability:** Shelf life stability studies of the intact bottles are on-going.

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

9.1.7 **Potential Drug Interactions:** Metabolism: Data from *in vitro* metabolism experiments in human tissues 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 microsomes (Acharya 2006). While inhibition of CYP enzymes 2B6 and 3A4 was seen, the data show that the degree of the inhibition makes it unlikely that any *in vivo* systemic interactions would occur. Intestinal CYP 3A4 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 substrate for P-gp and BCRP transporters, but did not inhibit either of these transport proteins.

9.1.8 **Patient Care Implications:** Entinostat may cause fatigue or malaise; advise patient to exercise caution while driving a vehicle or operating machinery.

Administration of entinostat is contraindicated in patients with a history of allergy to entinostat or other medications 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. (Section 3.1.1)

9.2 Medroxyprogesterone Acetate

Sites must refer to the package insert for detailed pharmacologic and safety information.

Product description: Medroxyprogesterone acetate injection contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder that is stable in air and that melts between 200° C and 210° C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-.

Medroxyprogsterone Injection for intramuscular (IM) injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

Each mL contains:

Medroxyprogesterone acetate

Polyethylene glycol 3350 Polysorbate 80

Sodium chloride Methylparaben Propylparaben

Water for injection

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

Solution preparation (how the dose is to be prepared): Refer to the package insert for standard preparation instructions.

Route of Administration: Medroxyprogesterone acetate is given as a single intramuscular (IM) dose. Either the vial or the prefilled syringe should be vigorously shaken just before each use to ensure that the dose being administered represents a uniform suspension. The injection should be given as a deep IM injection in the gluteal or deltoid muscle.

Availability/Supply: The agent is commercially available. Institutions may receive up to $250 per patient for cost of medroxyprogesterone acetate. See Funding Sheet for more information.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Pathology Review Guidelines

Not applicable.

10.2 Biospecimen Selection for Integral Biomarker Testing

Not applicable

10.3 Biospecimen Selection for Integrated Biomarker Testing

10.3.1 Biomarker to be Tested

Progesterone receptor (PR) and Ki67
As described in the preliminary data (Section 2), progestins result in endometrial differentiation and are useful in the treatment of endometrial cancer. Our principal translational goal is to test the hypothesis that the addition of entinostat, an epigenetic agent, will amplify the therapeutic effectiveness of MPA as determined by integrated molecular biomarkers of differentiation and response.

Progestins bind to the progesterone receptor (PR) and activate downstream genes involved in epithelial cell growth arrest including the cyclin dependent kinase inhibitor p21. In turn, Ki67 levels, a well-established marker for proliferation, are predicted to decrease significantly. Thus, we have chosen these two predictive markers, PR and Ki67, as integrated readouts of molecular response for this trial.

10.3.2 **Testing Requirements and Reporting**
Formalin-fixed, paraffin-embedded (FFPE) primary tumor tissue must be submitted for PR and Ki67 immunohistochemistry. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

10.3.3 **Method of Testing**
Immunohistochemistry
A polymer-based detection system with Dako autostainer and the FDA 510(k)-cleared pharmDx assay kit (Dako, Glostrup, Denmark) will be used. Please see the appended specific IHC protocols for PR and Ki67 as integrated biomarkers.

Antibodies
Antibody dilutions will be according to the manufacturer's recommendations.
PR: Mouse monoclonal antibody PgR636, 1A6, and Dako-PR
Ki67: Clone MIB-1 from Dako

Test Report Range
Positive results for all biomarkers require at least 1% of tumor cells express the biomarker. Tumors with less than 1% staining are considered negative. For PR, the degree of positivity will be determined according to College of American Pathologists/ASCO guidelines using the modified H score (percent of cells staining x intensity [1 to 3+], converted to a continuous variable). For Ki67, the number of positive staining nuclei per high power field averaged over 3 fields will be evaluated.

Invalid Test Results
Invalid test results include no tumor, wrong diagnosis, and lack of staining or nonspecific staining using the positive control tissue. If a specimen contains no tumor or the tumor is not determined to be an endometrioid endometrial carcinoma, the patient will be excluded from the analysis. If immunostaining results are non-specific or negative using the positive control run with each cycle, the immunohistochemistry will be repeated.

10.3.4 Location of Testing
Each month, the NRG Oncology Biospecimen Bank (NRG BB)-Columbus will batch

ship seven fresh cut unstained sections (charged, 4µm) to Dr. Megan Samuelson (Central Pathology Core Laboratory, University of Iowa). The Central Pathology Core Laboratory is CLIA certified and College of American Pathologists (CAP) accredited.

10.3.5 Biospecimen Submission for Testing

FFPE tumor blocks (or seven unstained sections [charged, 4µm]) must be shipped to the NRG BB-Columbus. **Unstained sections must be shipped to the NRG BB-Columbus immediately after sectioning.** See Mandatory Biospecimen Submission Table (section 10.4.1) for details. **Note: The time from surgical removal to processing (i.e., time in formalin) should be documented on Form TR (i.e., Estimated Processing Time). For optimal assessment of molecular markers, this time should be less than one hour.**

10.4 Biospecimen Submission Tables

Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment.

A detailed description of biospecimen procedures can be found in Appendix IV.

10.4.1 Mandatory Biospecimen Submissions

The patient must give permission to participate in this mandatory study component. Participating sites are required to submit the patient's biospecimens as outlined below.

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship Biospecimens To
FFPE Pre-treatment Primary Tumor (FP01)[1] 1st Choice: block 2nd Choice: 17 unstained fresh cut sections (charged, 4µm)[2]	Collected during D&C or biopsy, prior to study treatment.[3]	NRG Oncology BB-Columbus within 8 weeks of registration[4]
FFPE Post-treatment Primary Tumor (FP02)[1] **(at least 80% tumor required)** 1st Choice: block 2nd Choice: 17 unstained fresh cut sections (charged, 4µm)[2]	Collected during hysterectomy or BSO, after receiving study treatment.[3]	NRG Oncology BB-Columbus within 12 weeks of registration[4]

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus.
2 Unstained fresh cut sections must be shipped to the NRG BB-Columbus immediately after sectioning.
3 The time from surgical removal to processing (i.e., time in formalin) should be documented on Form TR (i.e., Estimated Processing Time). For optimal assessment of molecular markers, this time should be less than one hour.
4 NRG Oncology BB-Columbus / Protocol NRG-GY011, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.

10.4.2 Optional Biospecimen Submissions

If the patient gives permission to participate in this optional study component, then participating sites are required to submit the patient's biospecimens as outlined below.

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship Biospecimens To
Snap Frozen Post-treatment Primary Tumor (RP01)[1] at least 0.2g in foil	Collected during hysterectomy or BSO, after receiving study treatment[2]	NRG Oncology BB-Columbus within 4 weeks of registration[3]

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-

Columbus.
2 The time from surgical removal to freezing should be documented on Form TR (i.e., Estimated Processing Time).
3 NRG Oncology BB-Columbus / Protocol NRG-GY011, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.

10.5 Exploratory Biomarker Laboratory Testing

Note: Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

10.5.1 Immunohistochemistry

Pre- and post-treatment FFPE will be used to assess p21, PRB, ER, amphiregulin, FOXO1, and methylation markers indicative of HDACi activity. The NRG Oncology Biospecimen Bank (NRG BB)-Columbus will batch ship ten unstained sections (charged, 4μm) to Drs. Kimberly Leslie and Shujie Yang (University of Iowa).

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable.

12. ASSESSMENT OF EFFECT

No clinical evaluation criteria or endpoints are applicable to this protocol. The evaluation criteria are histologic, immunohistochemical and molecular as indicated below.

12.1 Histologic Response

An endpoint of the study is the histologic response (complete or partial) in endometrial adenocarcinomas 21-24 days following administration of medroxyprogesterone acetate with or without entinostat. The slide from the initial sample will be compared to the slide from the matching hysterectomy specimen without knowledge of treatment given.[18, 23]

12.1.1 Complete Histologic Response: indicates the presence of diffuse glandular secretory change, involution or atrophy, with loss of mitotic activity, and presence of stromal decidualization throughout the tumor sample from the hysterectomy.

12.1.2 Partial Histologic Response: represents a mixture of foci with glandular secretion or atrophy, loss of mitotic activity, and the presence of stromal decidualization, and foci of persistent adenocarcinoma with cell stratification, nuclear pleomorphism, mitoses, and the absence of stromal decidualization.

12.1.3 No Histologic Response: reflects the diffuse persistence of histologic features diagnostic of adenocarcinoma.

12.2 Steroid Receptor, Ki67 and p21 Status

This trial incorporates three integrated biomarkers, PR, Ki67 and p21.

Immunohistochemical staining for PR (integrated biomarker) and ERα (exploratory biomarker) will be evaluated in a semi-quantitative manner following the initial work of Carcangiu et al and Chambers et al, who demonstrated excellent correlation in the assessment of ERα and PR level using immunohistochemistry compared with biochemical methods such as ligand binding.[2, 3] The College of American Pathologists guidelines will be followed.[7] An experienced pathologist will review each slide in a blinded fashion and indicate the percent of immunopositive tumor cells. Per the guidelines, at least 1% of the cells in the specimen must be immunoreactive to consider the tissue positive. The intensity of staining (1+ to 3+ will also be scored, using the positive control tissue sample as 3+. +. Two additional pathologists (the chair and co-chair of the Pathology Committee) will independently review a sample of 50 slides to provide an estimate of the interobserver variability (see Sections 12.2.1, 12.2.2, and 12.2.3 for scoring). If the reproducibility is less than 90%, then a complete review of all steroid receptor immunohistochemistry may be performed. In general, the technique provides reliable semi-quantitation of receptor expression using a review and scoring method now employed by most academic health centers on clinical reports.

Ki67 is a nuclear protein that is tightly linked to the cell cycle. It is a marker of cell proliferation and has been used to stratify good and poor prognostic categories in invasive breast cancer and other tumor types. Immunostaining for Ki67 using the MIB-1 antibody strongly correlates with expression of the *Ki67* gene and with tumor invasiveness and inhibition of apoptosis[11]. Immunohistochemistry for Ki67 is an integrated biomarker for this trial. Ki67 protein expression is predicted to be down-regulated in endometrial cancer cells in response to activated PR and histologic response. Immunohistochemistry scoring will be carried out by assessing the number of cells with positive nuclear staining/high power field (averaged over 3 fields) as previously performed for Study GOG-0211.

The third integrated biomarker for this trial is $p21^{WAF}$/Cip1/Sdi1/Pic1, a cyclin-dependent kinase inhibitor and tumor suppressor, induced by progesterone through activated PR. This assay will be used to indicate PR transcriptional activity. Immunohistochemistry for p21 will be scored using the percent of cells staining positively X the intensity of staining (1+ - 3+) using colon cancer specimens as a positive control.

12.2.1 PR or ERα Negative: when less than 10% of the tumor cells exhibit nuclear staining for PR or ERα, respectively.

12.2.2 PR or ERα Positive: when 10-50% of the tumor cells exhibit nuclear staining for PR or ERα, respectively.

12.2.3 Strongly Positive for PR or ERα: when greater than 50% of the tumor cells exhibit nuclear staining for PR or ERα, respectively.

13. DATA AND RECORDS

13.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization rosters at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. See Sections 7.2 and 7.5 for information about expedited and routine reporting.

For reporting of second primary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

Summary of Data Submission: Refer to the NRG website [*Insert weblink to data submission summary]* for the table of Required Forms and Materials.

13.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Monitoring Method for Protocol NRG-GY011: CDUS Abbreviated

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

The overall objective of this study is to assess the short-term biologic activity of an HDAC inhibitor preceded by progestin in comparison to progestin alone in patients newly diagnosed with endometrioid endometrial carcinoma. This study is designed as a two-arm, open label, randomized, surgical window trial with a short term medroxyprogesterone acetate reference arm and an experimental arm of short term medroxyprogesterone acetate followed by entinostat (given over three doses). Treatment will be given prior to standard of care surgery, hysterectomy, to test the validity of the proposed mechanism of action of entinostat in the short term.

Prior to patient registration, eligibility will be reviewed by Entry Form verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. Patients will be registered by the participating site through OPEN and randomization will be carried out centrally by the NRG Statistics and Data Management Center. Treatment group assignment will be determined using a procedure that tends to randomly allocate study treatment s at a 1 to 1 ratio.

Reports and publications will include a complete accounting of all patients registered to this study.

14.2 Study Endpoints

Primary endpoint:

- The mean post-treatment tumor progesterone receptor score (percent cells staining positive multiplied by the staining intensity) compared between treatment arms to evaluate the association of the addition of entinostat treatment on tumor progesterone receptor expression.

Secondary endpoints:

- The difference in the proportion of patients with a histologic tumor response (complete or partial) between treatment arms.
- The mean post-treatment tumor Ki67 positive cell counts compared between treatment arms.
- The frequency and maximum severity of acute drug emergent and post-surgical adverse events by treatment arm as graded and categorized by CTCAE v4.0.

Exploratory endpoints

- The mean post-treatment tumor estrogen receptor score (percent cells staining

positive multiplied by the staining intensity) compared between treatment arms.
- The mean post-treatment tumor p21 receptor score (percent cells staining positive multiplied by the staining intensity) compared between treatment arms.
- Co-expression of PR, Ki67 and p21 compared between the treatment arms (an increase in PR, accompanied by a decrease in Ki67 and an increase in p21)

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

The design will provide a direct assessment of the null hypothesis that there is no difference in mean post-treatment tumor progesterone receptor scores in those treated with progestin followed by entinostat compared with those treated with progestin alone.

14.3.2 How Primary Endpoints Will Be Analyzed

A treatment difference in the distribution of post-treatment progesterone receptor scores will be tested using a Mann-Whitney test.

14.3.3 Sample Size and Power Calculations:

A sample size of 40 patients (20 in each treatment group) with associated evaluable pre- and post-treatment specimens will be targeted for testing for a treatment difference in the distribution of post-treatment progesterone receptor scores using a Mann-Whitney test. Type I error is set at 0.05 for a two-sided hypothesis test. Data from GOG-0211 were used to set the design assumptions.[22]It is assumed that progestin treatment alone will result in a down regulation of receptor levels from a mean of 1.7 pre-treatment to a mean of 0.7 post-treatment (mean score decrease of 1.0). With 40 evaluable participants there is 90% power to detect a treatment difference of -1.0 assuming a standard deviation of 0.8 in the reference group and 1.0 in the experimental treatment group. A primary endpoint inevaluability rate of 20% of patients enrolled is planned for due to the expectation that some assay results will be inevaluable or non-compliance with treatment. Thus a total sample size of 50 patients is planned to achieve the primary objective of this study with the desired precision and error tolerance.

The primary analysis will adhere to the intention-to-treat principle for those with evaluable specimens; this is expected to be equally likely on each arm. A sensitivity analysis will be performed by removing patients on the experimental arm that do not receive at least two doses of entinostat. This sensitivity analysis is intended to evaluate the effect in an idealized subgroup recognizing that removing these patients through a non-random process can lead to bias since we cannot identify cases on their counterparts on the reference arm.

Other testing procedures were considered. For example, an ANCOVA model could be used to test the treatment difference while adjusting for pre-treatment progesterone receptor scores or testing the mean post-treatment – pre-treatment differences could be compared between arms with a T test. T tests are generally less powerful than ANCOVA. The ANCOVA model and a T test require paired samples from each individual. Stronger assumptions about normality of model residuals are required that do not appear to hold (see histograms in Figure S1). Further ANCOVA assumptions

presume that there is a linear relationship between pre- and post-test scores and equal variances between treatment groups. Finally, the correlation between pre- and post-treatment samples is only 0.3 (Table S1) and adjustment for baseline levels in an ANCOVA model will only account for 9% of the within group variance. An ANCOVA model can be fit to the data as an exploratory analysis to estimate the difference in post-treatment progesterone receptor means accounting for the pre-treatment scores after assessment of assumptions and adjustments for departures from the assumptions.

Table S1. Mean, standard deviation and correlation of pre- and post-treatment progesterone receptor from GOG-0211

	Sample Size	*Sample Mean*	*Sample Standard Deviation*	*Sample Correlation*
Pre-treatment progesterone receptor score	53	1.78	1.02	0.3
Post-treatment progesterone receptor score	53	0.66	0.80	

Figure S1. Histograms and scatter plots of pre- and post-treatment progesterone receptor scores from GOG-0211

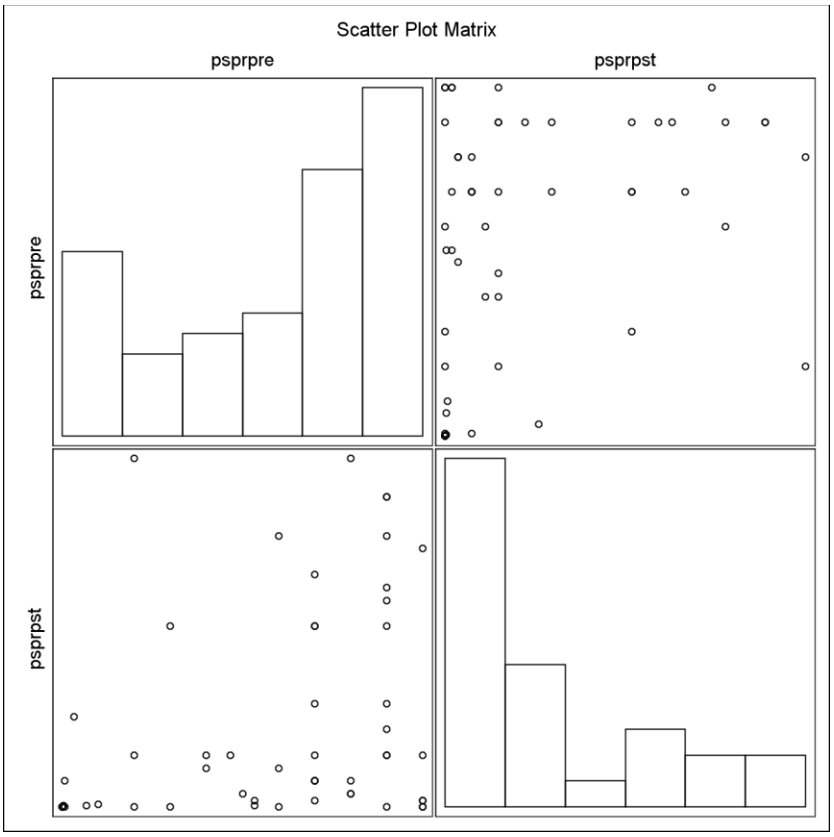

Table S2. Sample Sizes for Various Two Sample Tests – the largest sample size was chosen to accommodate possible scenarios

Test (Distribution)	***N1***	***N2***
T Test	19	19
M-W Test (Uniform)	19	19
M-W Test (Logistic)	18	18
M-W Test (Normal)	**20**	**20**
ANCOVA (Normal)	17	17

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1<>Mean2
N1 and N2 are the number of patients in each treatment group.
Calculations were done using PASS 2008 version 08.0.16 release date: January 27, 2011.[9]

Simulation results using historical post-treatment data are consistent with the power calculations under test assumptions.

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. There is no formal interim analysis planned. The DMC may also elect to review the study on an "as needed" basis.

14.5 Accrual/Study Duration Considerations

Between 1/2005 and 9/2008, accrual on GOG-0211 averaged 18 enrollments per year; at its maximum it was 30 per year. The expected annual rate is 18 per year over 3 years without any interruptions; this includes a 3 month start-up time with little to no accrual. Operationally, accrual will automatically be paused by OPEN when the 50th patient is enrolled. Final analysis will require distribution of specimens, resolution of queries, completion of all laboratory tests, and collation of laboratory data with clinical data. These can be accomplished within 6-12 months of final patient entry.

14.6 Dose Level Guidelines

There are no dose level changes defined in this study.

14.7 Secondary or Exploratory Endpoints (including correlative science aims)

14.7.1 Secondary Hypotheses and Endpoints:

There will be an assessment of the null hypothesis that there is no difference in proportion of patients with a complete or partial histologic tumor response and Ki67 expression in those treated with progestin followed by entinostat compared with those treated with progestin alone.

Data from GOG-0211 suggest that responders will have a significant decrease in Ki67 expression (approximately 50% decrease in the average number of cells staining positive

for Ki67) when compared to non-responders (22% decrease) when treated with medroxyprogesterone acetate. With the addition of entinostat, the number of responders is expected to increase and Ki67 is expected to be lower.

Based on data from GOG-0211, the mean number of cells staining for ki67 post treatment ki67 is estimated to be 136 with a standard deviation of 119. There is 80% power to detect a treatment difference of 80 (mean of 56) using a Mann-Whitney test with 42 patients equally allocated and setting type 1 error to 10%. Power to detect this difference with 40 patients is 78%.

14.7.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Similar testing procedures as used for the primary endpoint can be applied to Ki67 scores. A confidence interval around the estimate of the treatment difference in the proportion with a histologic response will be constructed. Correlation between Ki67 and histologic response will be evaluated by treatment arm.

The frequency and maximum severity of acute drug emergent and post-surgical adverse events will be tabulated by treatment arm as graded by CTCAE v4.0.

14.7.3 Monitoring of Adverse Events

Clinical data collected on this protocol will be reviewed by the study data manager and will also be reviewed by the Study Chairperson in conjunction with the Statistics and Data Management Center (SDMC) on an ongoing basis. In some instances, because of unexpectedly severe toxicity, early closure of a study may be elected.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the study chairperson, disease site committee and the committee charged with monitoring safety in conjunction with each semi-annual meeting.

All serious adverse events (SAEs) are reported to the Study Chair, Sponsor, Pharmaceutical Company, and regulatory agencies as mandated in the protocol. SAE reports are reviewed by the Study Chair (or designated co-chair) immediately for consideration of investigator notification of a suspected unexpected serious adverse reaction (SUSAR), protocol amendment, and/or immediate study suspension. All participating institutions will receive notification of the SUSAR from NRG as well as the reason for study suspension (if applicable). Under these circumstances, accrual cannot be re-activated until the study is reviewed by the committee charged with monitoring safety. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

14.8 Gender/Ethnicity/Race Distribution

The expected enrollment data is based on accrual from GOG-0210.

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	0	0	0	1
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	6	0	0	0	6
White	40	0	2	0	42
More Than One Race	0	0	0	0	0
Total	48	0	2	0	50

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APPENDIX I – 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 II- NYHA CLASSIFICATION

Congestive Heart Failure – New York Heart Association Classification

Class	Definition
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964: 114.

APPENDIX III – COLLABORATIVE AGREEMENT

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.

APPENDIX IV – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES

I. Obtaining a Bank ID for Translational Science Biospecimens

Only one Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component. If a patient has previously been assigned a Bank ID, please ensure the Bank ID appearing in Rave is the same as the previously assigned Bank ID.

Please contact User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@nrgoncology.org; Phone: 716-845-7767).

II. Requesting Translational Science Biospecimen Kits

One single chamber kit will be provided per patient for the collection and shipment of frozen tissue.

Sites can order kits online via the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement). Each site may order two kit types per protocol per day (daily max = 6 kits).

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

Note: Unused materials and kits should be returned to the NRG BB-Columbus.

III. FFPE Shipped to the NRG BB-Columbus

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (i.e., primary tumor).

Pre-treatment primary tumor (FP01) should be collected from D&C or biopsy prior to treatment.

Post-treatment primary tumor (FP02) should be collected during hysterectomy or BSO.

Only one block may be submitted per tissue type.

All FFPE tissue should be submitted with the corresponding pathology report.

Every attempt should be made to provide an FFPE block; however, if a block cannot be provided on a permanent basis, then 17* unstained sections (charged, 4µm) should be submitted. **If submitting unstained sections, your pathology department must cut fresh 4µm sections**

sequentially from one block at the time of your request. These fresh cut sections must be shipped to the NRG BB-Columbus within 48 hours of sectioning.

**Seven unstained slides (charged, 4µm) must be shipped to the NRG BB-Columbus to satisfy the mandatory biospecimen requirement for integrated biomarker testing.*

Completing Form TR for FFPE Biospecimens

- The type of biospecimen (block, slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.
- **The time from surgical removal to processing (i.e., time in formalin) should be documented on Form TR (i.e., Estimated Processing Time). For optimal assessment of molecular markers, this time should be less than one hour.**

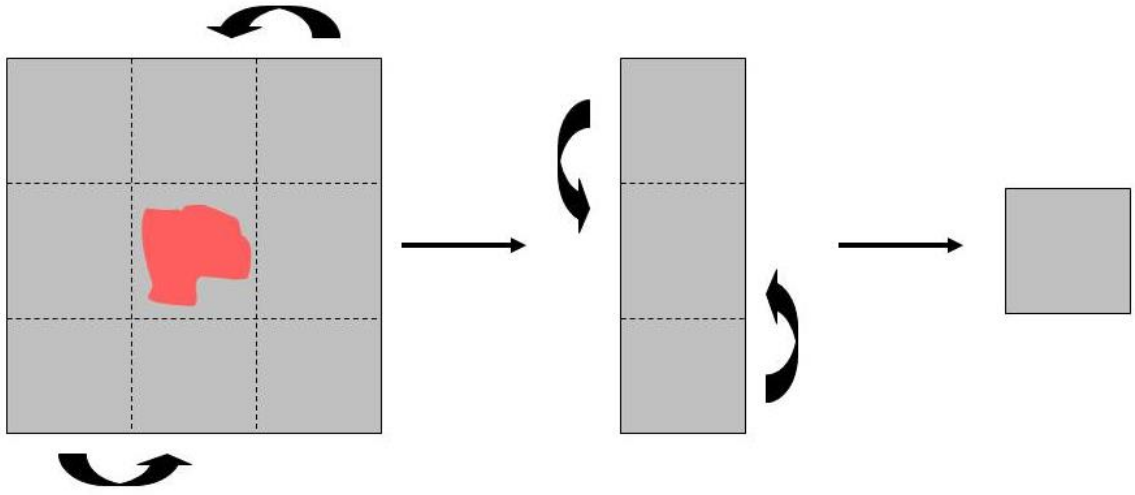
Labeling FFPE Tissue

A waterproof permanent marker or printed label should be used to label each translational science tissue biospecimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG - GY # # #)
specimen code (see above)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

IV. Frozen Tissue Shipped to the NRG BB-Columbus



1. Label the zip-lock bag as described below. If using an adhesive label, place it inside the bag.
2. Snap freeze tissue within 15 minutes after surgery for optimal preservation. Place tissue on a piece of foil and fold foil around tissue as shown in diagram below. Snap freeze tissue on dry

ice or in the vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen). If neither dry ice nor liquid nitrogen is available, slow freeze tissue in a -70°C to -80°C freezer.

3. Once the tissue is frozen, place in pre-labeled zip-lock bag.
4. Immediately store snap frozen tissue in a liquid nitrogen freezer (at vapor phase), a -70°C to -80°C freezer, or by direct exposure with dry ice until ready to ship.

Completing Form TR for FFPE Biospecimens

- **The time from surgical removal to freezing should be documented on Form TR (i.e., Estimated Processing Time).**

Labeling Frozen Tissue

A waterproof permanent marker or printed label should be used to label each translational science tissue biospecimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG - GY # # #)
specimen code (see protocol section 10.4.2)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

V. Submitting Form TR

An electronically completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus. Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the NRG BB-Columbus if biospecimens are not collected.

Form TR should be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a single page PDF. Do not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@nrgoncology.org; Phone: 716-845-7767).

VI. Shipping Translational Science Biospecimens

Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each translational science biospecimen.

A. FFPE Tissue
FFPE tissue* and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

NRG BB-Columbus / Protocol NRG-GY011
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

Upon receipt at the NRG BB-Columbus, all unstained sections will be vacuum sealed.

B. Frozen Tissue
Frozen tissue, including a copy of the corresponding pathology report for frozen tissue, should be shipped using the biospecimen kits provided to the NRG BB-Columbus (address above).

Frozen biospecimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen biospecimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen biospecimens.

Frozen biospecimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the biospecimens can be shipped.

Shipping Frozen Translational Science Biospecimens in a Single Chamber Kit
1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen biospecimens a s zip-lock bag.
3. Place the zip-lock bag in the biohazard envelope containing absorbent material. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR and corresponding pathology report for the biospecimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement). Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

VII. Banking Translational Science Biospecimens for Future Research
Biospecimens will remain in the NRG BB-Columbus and made available for approved research

projects if the patient has provided permission for the use of her biospecimens for future health research.

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her biospecimens at any time if the patient changes her mind.

If the patient revokes permission to use her biospecimens, the NRG BB-Columbus will destroy or return any remaining biospecimens. The patient's biospecimens will not be used for any <u>further</u> research; however, any biospecimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her biospecimens distributed prior to revoking consent.

Note: If return of biospecimens is requested, shipping will be at the site's expense.