NRG ONCOLOGY
NRG-GY008
(ClinicalTrials.gov NCT #02728258)
A PHASE II EVALUATION OF COPANLISIB (BAY 80-6946) (IND #130822), A SELECTIVE INHIBITOR OF PI3KCA, IN PATIENTS WITH PERSISTENT OR RECURRENT ENDOMETRIAL CARCINOMA HARBORING PIK3CA HOTSPOT MUTATIONS
NCI Version Date: 03/21/2017

This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.
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This study is limited to NRG Oncology participation

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Participating Sites

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NRG-GY008
SCHEMA (01/09/2017)

Patients with recurrent or persistent endometrial cancer with PIK3CA mutation as determined by Roche COBAS® PIK3CA Mutation Test

(See Section 3 for specific eligibility criteria.)

Copanlisib (BAY 80-6946) 60 mg IV weekly, Days 1, 8 and 15 of a 28-day cycle (3 weeks on/1 week off) until disease progression or adverse effects prohibit further treatment.

1. OBJECTIVES

1.1 Primary Objective

To assess the activity of copanlisib (BAY 80-6946) in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA hotspot mutations with the frequency of objective response.

1.2 Secondary Objectives

1.2.1 To estimate 6 month progression-free survival (PFS) and median PFS

1.2.2 To estimate the distribution of the duration of overall survival (OS)

1.2.3 To assess the safety profile of copanlisib in endometrial cancer patients

1.3 Exploratory/Correlative Objective

To systematically evaluate by sequencing the site (i.e., exome) and characteristics of PIK3CA mutations in endometrial cancer patients and correlate such mutations to overall response (OR), PFS, and OS in patients treated with copanlisib.

2. BACKGROUND

Endometrial cancer is the most common gynecologic malignancy with approximately 54,870 new cases and 10,170 estimated deaths related to the disease in the United States annually.[1] Endometrial cancers have historically been designated as Type I or Type II.[2] Type I endometrial cancer accounts for 65-70% of cases and is associated with grade 1-2 endometrioid histology, younger age of onset, retention of estrogen receptor (ER) and progesterone receptor (PR) status, a history of unopposed estrogen, and deletions in k-Ras, PTEN, or mismatch repair mechanisms.[2,3] In contrast, Type II endometrial cancer is associated with serous, clear cell or grade 3 endometrioid histology, loss of ER/PR, black race, absence of unopposed estrogen, presentation at later stage, reduced E-cadherin expression, aneuploidy, mutations in p53 and HER2/Neu overexpression.[2-4] Type II endometrial cancer is typically more aggressive than type I cancer and has a poorer prognosis. Recently, using an integrated genomic, epigenomic, transcriptomic and proteomic approach, The Cancer Genome Atlas (TCGA) Research Network provided compelling evidence that endometrial cancers result from heterogeneous somatic mutations and, accordingly, classified endometrial cancers into four categories: 1) polymerase epsilon (POLE)-ultramutated, 2) microsatellite instability hypermutated, 3) copy-number low and 4) copy-number high, serous-like.[5] The genetic aberrations of endometrial carcinomas may therefore represent a novel tool to classify these tumors and guide adjuvant treatment in women with recurrent chemotherapy-resistant disease.

The phosphatidylinositol-3-kinase (PI3KCA) gene encodes for a heterodimeric protein with an 85-kDa regulatory subunit (PI3KR1) and a 110-kDa catalytic subunit (PI3KCA).[6] PI3K phosphorylates a series of membrane phospholipids, catalyzing the transfer of ATP (adenosine triphosphate)-derived phosphate, thereby forming secondary messenger lipids phosphatidylinositol3,4-bisphosphate and phosphatidylinositol3,4,5-trisphosphate and initiating the downstream AKT/mTOR signaling cascade that regulates cell growth.[6] The

central role of PI3K activation in tumor cell biology has prompted an effort to target PI3K and/or downstream kinases such as AKT and mammalian target of rapamycin (mTOR) in endometrial cancer.[7] Consistent with this view several research groups have recently reported the activity of multiple PI3KCA and mTOR inhibitors in endometrial cancer in preclinical studies. For example, apitolisib (GDC-0980, Genentech, South San Francisco, CA), a potent inhibitor of class I PI3K and mTOR kinase (TORC1/2), has shown significant activity in vitro and in vivo against biologically aggressive endometrial tumors harboring PI3K driver mutations.[8] Furthermore, AZD8055, a novel dual mTORC1/2 inhibitor, demonstrated significant tumor growth inhibition in high HER-2/neu-expressor endometrial cancers in vitro[9] as well as in vivo regression in breast, lung, colon, prostate, and uterine xenograft models.[10] Taselisib, GDC-0032 (Genentech, South San Francisco, CA), a novel, oral, selective inhibitor of PI3KCA, has been shown to be highly active in uterine serous carcinoma (USC) mouse xenografts harboring PI3KCA mutations and overexpressing HER2/neu ($p = 0.007$).[11] Finally, copanlisib (BAY80-6946), a novel PI3K-alpha and delta-inhibitor with promising early clinical signal of activity in heavily pretreated patients including endometrial cancer patients in Phase I studies, has shown remarkable activity against multiple primary endometrial cancer cell lines harboring PI3K driver mutations (Figure 1 below and Santin AD, unpublished data).
(01/09/2017)

Multiple phase I, II, and III clinical trials with inhibitors targeting PI3K, AKT or mTOR pathways are currently ongoing or have been recently completed.[12] Unfortunately, emerging clinical data show limited single-agent activity of these inhibitors at tolerated doses.[13-15] However, it is important to note that the response rate for patients with heavily-pretreated, advanced cancers and PI3KCA mutations who were given PI3K/AKT/mTOR axis inhibitors was significantly higher than that for patients without documented PI3KCA mutations treated on the same trials.[13-15] This observation is consistent with data that demonstrate low response rates on traditional phase I and II trials, in which molecular testing is not used, and suggests that selecting PI3KCA-mutant patients for treatment with PI3K/AKT/mTOR axis inhibitors may potentially predict response. Importantly, in endometrial cancers multiple studies have shown that unlike other human tumors, PI3KCA mutations are distributed throughout the gene. Consistent with this view, Rudd et al.,[16] reported that half (29 of 58) of non-synonymous PIK3CA mutations in Type I and Type II cancers are located in exons 1-7 while half are in exons 9 and 20 (i.e., known hotspot mutations). Importantly, the exons 1-7 mutations have been shown to localize to the ABD, ABD-RBD linker and C2 domains of p110α and similarly to the hot spot mutations located in exon 9 and 20, may increase the levels of phospho-AKTSer473 compared to wild-type p110α.[16] Taken together, these data suggest that in endometrial cancer patients PI3KCA mutations located outside exons 9 and 20 may also represent potential targets for selective pan-Class I PI3K inhibitors such as copanlisib (BAY 80-6946).

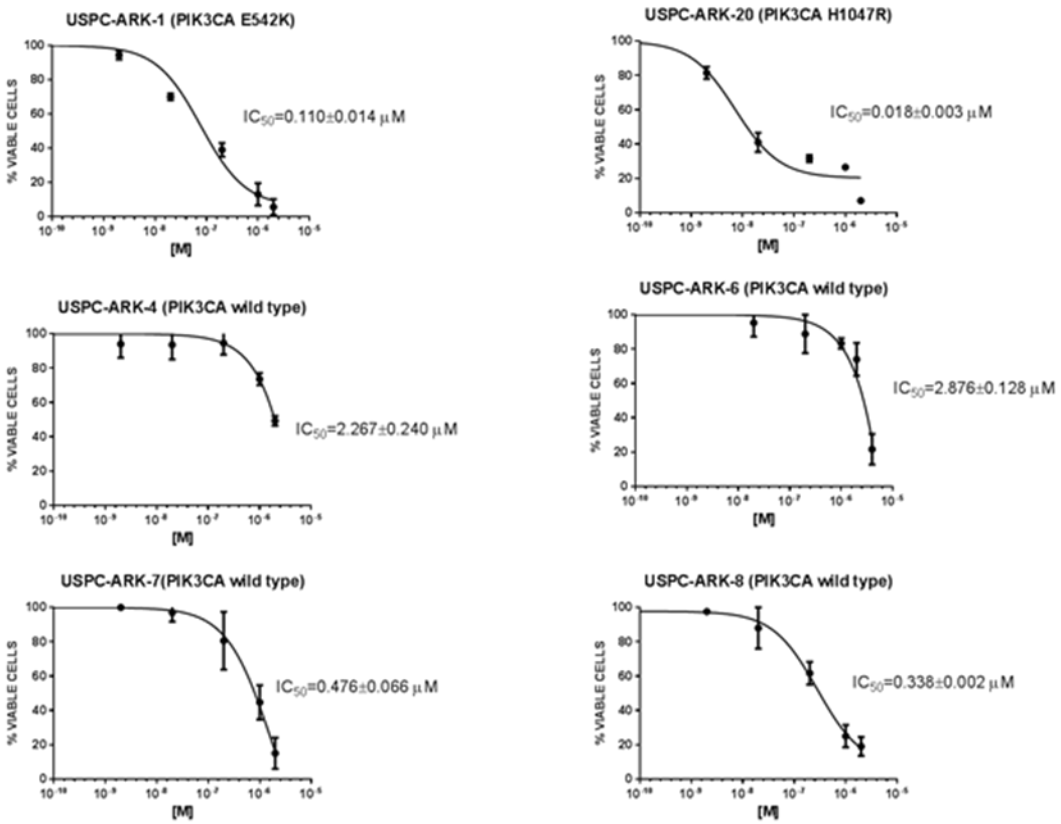

Figure 1: Representative dose response curves with IC_{50} of two PI3KCA mutated endometrial cancer cell lines [USPC-ARK-1 (E542K) and USPC-ARK-20 (H1047R)] versus four PI3KCA wild-type cell lines after in vitro exposure to BAY80-6946 for 72 hrs. As shown in figure 1, PI3KCA mutated endometrial cancer cell lines were found to be significantly more sensitive than PI3KCA wild-type cell lines to BAY80-6946 (P=0.004). Similar results were obtained when UTE4 (i.e., a poorly differentiated endometrioid adenocarcinoma cell line harboring the R88Q mutation in exon 1 (ref. 17 and data not shown), was exposed in vitro to BAY80-6946. The results with copanlisib are in full agreement with recently published preclinical data obtained exposing a large number of primary endometrial cancer cell lines to others mTOR/PIK3CA inhibitors (i.e., AZD8055, GDC-0980, GDS-0032).[8, 9, 11]

Copanlisib (BAY 80-6946) is an intravenous, potent and highly selective pan-Class I PI3K inhibitor showing superior antitumor activity (>40-fold) in PI3KCA mutant tumors in preclinical studies and promising clinical activity and manageable toxicity in Phase I and II clinical trials.[18-20] Most common side effects of copanlisib in phase I/II clinical studies included hyperglycemia and transient Grade 3 or 4 hypertension in up to 43% of the patients. Copanlisib not only inhibits PI3Kα with IC50 of 0.5 nM, but also PI3Kδ with IC50 of 0.7 nM. In vivo, single intravenous administration of copanlisib exhibited higher exposure and prolonged inhibition of pAKT levels in tumors versus plasma. Copanlisib also potently regulates nuclear localization of the forkhead family members resulting in the induction of transcriptional programs that lead to rapid cell death by apoptosis. Thus, copanlisib is a promising agent with differential pharmacologic and pharmacokinetic properties for the

treatment of PI3K-dependent human tumors. Because of the promising activity and tolerability of copanlisib in Phase I and II clinical trials, in the proposed Phase II study we are planning to evaluate the biological activity of copanlisib in patients with persistent or recurrent endometrial carcinoma harboring PI3KCA mutations. **(01/09/2017)**

2.1 Copanlisib (BAY 80-6946)

Class I PI3K is downstream of most cancer-associated tyrosine kinase growth factor receptors (such as epidermal growth factor receptor [EGFR]/ human epidermal growth factor receptor [HER], insulin-like growth factor 1 receptor [IGF-1R], platelet-derived growth factor receptor [PDGFR], vascular endothelial growth factor [VEGF], c-KIT or mesenchymal epithelial transition factor [Met]).

Four of these PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2) as a substrate to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and β are ubiquitous; PI3Kγ and δ are expressed mostly in the hematopoietic tissue.

Copanlisib (BAY 80-6946) is a potent pan-class I inhibitor of PI3K being developed for the treatment of advanced and refractory malignancies. Copanlisib is the active ingredient (free base) of BAY 84-1236, the dihydrochloride salt, which for clinical use is formulated as an intravenous (IV) drug product solution.

2.2 Clinical Experience

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of February 2015 approximately 377 patients with advanced cancer have been treated with copanlisib in eight different Phase I studies and one Phase II study.

2.3 Pharmacokinetics

Pharmacokinetic (PK) results of copanlisib indicate dose proportional increases in maximum concentration (C_{max}) and area under the curve (AUC) from time zero to 25 hours (AUC 0-25) in the dose range 0.1 to 1.2 mg/kg with a terminal phase half-life (t1/2) of 38.2 hours at 0.8 mg/kg (n=28). These data indicate that copanlisib is widely distributed in tissues and support a once weekly dosing regimen. No accumulation was observed after once weekly dosing when comparing PK on Cycle 1 Days 1 and 15 and Cycle 3 Day 15. No evidence of time-dependency in the PK of copanlisib was observed.

Preliminary results of the human ADME (absorption, distribution, metabolism, and excretion) study in healthy volunteers indicate that following a single intravenous dose of 12 mg [^{14}C]-BAY 80-6946, 88.3% of administered dose, with approx. 66.1% of dose excreted in feces, and approximately 22.2% of dose excreted in urine was recovered within 34 days. Copanlisib was found to be the primary circulating moiety in plasma as well as in excreta. The amount of copanlisib excreted unchanged amounts up to 40 to 50%. The morpholinone derivative M-1 was found to be the only relevant metabolite. Oxidative biotransformation of copanlisib was

found to be predominantly mediated by cytochrome P450 isoenzyme 3A4 (CYP3A4) and its contribution is about 50% of the metabolic pathway. Therefore, a low DDI potential due to several clearance pathways is anticipated.

A preliminary population PK analysis revealed no impact of either body weight, body surface area, or other body size-related factors was found on the clearance of copanlisib which was the basis to switch to a flat-dose regimen of copanlisib.

The recommended (Phase II) dose of monotherapy copanlisib is 60 mg given IV weekly (q1w) in a 3 weeks on/1 week off schedule based on an evaluation of pharmacokinetic and clinical data from ongoing single-agent studies.

2.3.1 Study 12871

A total of 68 cancer patients were enrolled in this open-label, single agent, Phase 1 dose-escalation study and 57 have received treatment. Copanlisib (BAY 80-6946) is infused intravenously over one hour on Days 1, 8, and 15, every 28 days. One cycle consists of 28 days. All 57 patients received at least one dose of copanlisib.

Seventeen patients were treated in the dose escalation part with five copanlisib dose levels: one in dose level 1 (0.1 mg/kg), three in dose level 2 (0.2 mg/kg), three in dose level 3 (0.4 mg/kg), seven in dose level 4 (0.8 mg/kg) and three in dose level 5 (1.2 mg/kg). Dose level 4 has been determined to be the MTD based on a dose level 5 patient with life-threatening cardiovascular toxicity following the first dose. Copanlisib (BAY 80-6946) has been generally safe and tolerable in patients treated through the MTD of 0.8 mg/kg. Forty patients have been enrolled in the MTD expansion cohorts, including 9 patients with NHL and 25 non-diabetics with solid tumors treated at the MTD, and 6 patients with solid tumors and type 2 diabetes mellitus treated at 0.4 mg/kg. Preliminary data on the diabetic patients has shown the tolerability of the 0.4 mg/kg dose, albeit with the requirement of additional diabetic specific therapy.

The overall median number of copanlisib infusions administered was 6 (range: 1 to 103 infusions). Although the protocol design permits intra-subject dose escalation for diabetic patients, none have received a dose greater than the starting dose of 0.4 mg/kg, due to progressive disease or AEs before Cycle 3 Day 1.

As of 10 FEB 2014, the most common drug-related TEAEs all grades, that occurred in ≥20% of the 57 patients (all cohorts) were: hyperglycaemia (36 patients, 63.2%); nausea (21 patients, 36.8%); and hypertension (12 patients, 21.1%). 0.8 mg/kg of copanlisib is the MTD in non-diabetic patients as single agent given intravenously in a 3 weeks on/1 week off schedule (total dose not to exceed 65 mg, in order to control copanlisib exposure in obese patients).

2.3.2 Study 12874

This is an open label Phase 1 study to determine the MTD and RP2D of copanlisib in combination with paclitaxel in patients with advanced cancer.

As of the cut-off date of 01 FEB 2015, a total of 83 patients were enrolled into this study and 55 were treated. Those 55 patients were treated in the following cohorts:

- Nineteen patients in the dose-escalation cohort received treatment with paclitaxel

given at the dose of 80 mg/m2 (as 60 min i.v. infusion) once weekly on Days 1, 8, 15, and 22 and copanlisib at the starting dose of 0.6 mg/kg as 60 min i.v. infusion (Cohort 1, 8 patients, of whom one did not receive copanlisib but paclitaxel only) or at the dose of 0.8 mg/kg (Cohort 2, 11 patients) once on Days 2, 9, 16, and 23. The MTD of copanlisib in combination with paclitaxel has been first determined as being 0.8 mg/kg given intravenously in a weekly schedule.

- Sixteen patients with breast cancer, were treated in the MTD expansion cohort (Cohort 3) received treatment with copanlisib in combination with gemcitabine and cisplatin (Treatment schedule B, copanlisib at 0.8 mg/kg). Due to the increased rate of the non-infectious pneumonitis observed in Cohort 3, a modified schedule of both copanlisib and paclitaxel was evaluated in order to establish the RP2D in combination with paclitaxel.
- Twenty patients with breast cancer treated in an expansion cohort with a modified dosing (Cohort 4) allowing a rest week between the cycles (3 weeks-on/1 week-off). Copanlisib is administered at 0.8 mg/kg on Days 2, 9 and 16 in the 28-day cycle. Paclitaxel is administered in the recommended 90 mg/m2 dose on Days 1, 8 and 15 in the 28-day cycle.

As the cut-off date of 01 FEB 2015, preliminary safety data indicate that the tolerable dose with the combination has been defined as being copanlisib 0.8 mg/kg on Days 2, 9 and 16 and paclitaxel administered at the dose of 90 mg/m2 on Days 1, 8 and 15, both in the 28-day cycle. The regimen with the continuous schedule of both drugs has been shown to bear a higher, not acceptable risk of non-infectious pneumonitis. The study is now closed for enrollment.

2.3.3 Study 12875

This open-label, Phase 1 study involves treating advanced solid tumor patients with copanlisib in combination with gemcitabine 1000 mg/m2 once on Days 1, 8, and 15, every 28 days (Treatment schedule A) or with gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 once on Days 1 and 8, every 21 days (Treatment schedule B). For Treatment schedule A, copanlisib dosing was started at a dose of 0.6 mg/kg and then 0.8 mg/kg was given once 0.6 mg/kg dose was tolerated (maximum dose). Once the MTD for Treatment schedule A was determined then Treatment schedule B using the MTD of copanlisib from Treatment schedule A was initiated along with the addition of cisplatin.

As of the cut-off date (01 FEB 2015), final data are not yet available from this study. A total of 65 patients were enrolled into this study and 50 were treated. Those 50 patients were treated in the following cohorts:

- Sixteen patients in the dose-escalation cohort received treatment with copanlisib in combination with gemcitabine (Treatment schedule A, n=8 at 0.6 mg/kg of copanlisib and n=8 at 0.8 mg/kg of copanlisib).
- Fourteen patients in the dose-escalation cohort received treatment with copanlisib in combination with gemcitabine and cisplatin (Treatment schedule B, copanlisib at 0.8 mg/kg). One patient in this cohort did not receive copanlisib but started gemcitabine.
- Twenty patients with BTC treated in the MTD expansion cohort.

The MTD of copanlisib is 0.8 mg/kg in combination with gemcitabine 1000 mg/m2 given

intravenously in a 3 weeks on/1 week off schedule as well as in combination with gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2, given intravenously in a 2 weeks on/1 week off schedule. There was one DLT of reversible posterior leukoencephalopathy syndrome (RPLS) in 1 patient treated at 0.6 mg/kg copanlisib in Treatment A. This study is now closed for enrollment.

2.3.4 Study 12876

This open-label, Phase 1 study involves treating advanced solid tumor patients with copanlisib in combination with refametinib. The study has been completed and closed. As the cut-off date of 01 FEB 2015, 64 patients received treatment with refametinib and the PI3K inhibitor (BAY 80-6946), including a dose escalation part (49 patients) and an MTD expansion cohort (15 patients). Nine dose cohorts combining increasing doses and varying schedules of copanlisib (0.2-0.8 mg/kg; given intravenously in a 3 weeks on/1 week off schedule or once weekly) and refametinib (30 mg and 50 mg bid p.o.; continuous or 4 days on/3 days off) on 28-day cycles were studied.

In the dose escalation part, 49 patients received at least one dose of study treatment, 48 patients were treated with at least one dose of copanlisib and refametinib (one patient received one dose of copanlisib but no refametinib). Fifteen patients were treated in a mutation selected expansion cohort in mixed solid tumors.

The most common copanlisib-related TEAEs that occurred in >20% of all patients were: diarrhea (30 patients, 46.9%); nausea (25 patients, 39.1%); hypertension (23 patients, 35.9%); hyperglycaemia and mucositis oral (20 patients, 31.3% each); fatigue (19 patients, 29.7%); vomiting (18 patients, 28.1%); rash maculo-papular and anorexia (14 patients; 22% each); and rash acneiform (20.3%). The most common refametinib-related TEAEs that occurred in >20% of the patients were: rash acneiform (33 patients, 51.6%); diarrhea (31 patients, 48.4%); nausea (26 patients, 40.6%); rash maculo-papular and mucositis oral (23 patients, 35.9% each); vomiting (20 patients, 31.3%); fatigue (18 patients, 28.1%); pruritus (16 patients, 25.0%); and anorexia (15 patients, 23.4%).

Dose-limiting toxicities (DLTs) included mucositis oral (3 patients); fatigue and aspartate aminotransferase (AST) increased (2 patients each); pancreatitis, diarrhea, rash acneiform, hypertension, and alanine aminotransferase increased (1 patient each). One patient with the DLT mucositis oral also experienced further DLTs nearly concomitantly: dehydration, dry skin, hypernatremia.

The MTD for the copanlisib-refametinib combination was 0.4 mg/kg copanlisib given intravenously in a weekly schedule and refametinib 30 mg bid given orally. These doses are below the MTDs of either compound alone: Copanlisib 0.8 mg/kg given intravenously in a 3 weeks on/1 week off schedule and refametinib 50 mg bid or 100 mg qd p.o.

2.3.5 Study 15205

Overall, 10 patients were treated in this open-label, single-agent, Phase 1 study of copanlisib in patients with advanced or refractory solid tumors, which was completed and closed in 2012. This study consisted of two cohorts (0.4 mg/kg, i.v., Day 1, 8, and 15, every 28 days for Cohort

1 and 0.8 mg/kg, i.v., Day 1, 8, and 15, every 28 days for Cohort 2). Three patients were treated in Cohorts 1 and 7 patients in Cohort 2, respectively.

The most common study drug-related TEAEs that occurred in >20% of all patients were hyperglycemia (80%), hypertension (70%), and constipation (50%). Based on pre-specified criteria in the protocol, the MTD was determined to be 0.8 mg/kg of copanlisib given as a single agent intravenously in a 3 weeks on/1 week off schedule in non-diabetic patients.

2.3.6 Study 16353

In this single center, non-randomized, open-label, non-controlled study, a total of 18 healthy male patients were enrolled and 6 received a 1-hour i.v. infusion of a single dose of 12 mg copanlisib containing 2.76 MBq [14C]copanlisib in a total volume of 40 mL. The aim of the study was to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics of copanlisib. This study was completed in 2014 and is now closed. A single i.v. infusion of 12 mg copanlisib over 1 hour was well tolerated by healthy male subjects.

2.3.7 Study 16790

This Phase I multicentric pharmacodynamic study of copanlisib aims to evaluate the relationship between exposure and pharmacodynamics in patients with NHL or selected solid tumors (with high likelihood of PI3K pathway activation such as breast cancer, ovarian cancer) after treatment with copanlisib monotherapy at the dose of 0.8 mg/kg body weight and 0.4 mg/kg (not to exceed 65 mg) for the non-diabetic patients as well as at the dose of 45 mg and 60 mg for the diabetic patients. A secondary objective is to assess the safety and tolerability of copanlisib in patients, including patients with diabetes mellitus. This study has started enrollment in 2014 and is still ongoing. So far, no safety concerns appeared.

2.3.8 Study 16349

Part A of the Study 16349 is an ongoing open-label uncontrolled, parallel group, signal-generating, Phase 2 study to evaluate efficacy and safety of copanlisib as single agent (0.8 mg/kg, maximum 65 mg, i.v. dosing over 1 hour on Days 1, 8, and 15 of each 28-day treatment cycle) in patients with relapsed or refractory, indolent or aggressive NHL. The study population was planned to consist of 2 cohorts of 30 patients each with either indolent lymphoma, or aggressive lymphoma. The patients are relapsed or refractory after ≥2 prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen), and must have received rituximab and alkylating agents. The primary efficacy variable is the objective tumor response (OR).

Part B of this study evaluates the efficacy and safety of copanlisib in patients with relapsed or refractory indolent NHL. As of the cut-off date of the IB (01 FEB 2015), a total of 244 patients were enrolled into this study, 166 in Part A and 78 in Part B. The cut-off date for the below reported data is 16 SEP 2014. As of the cut-off date (16 SEP 2014), 76 patients (33 with indolent and 43 with aggressive NHL) have started treatment in Part A and 42 patients in Part B. In the following preliminary sections, data from the ongoing Part A is presented. No data on Part B patients is available at this time.

As of 16 SEP 2014, a total of 76 lymphoma patients started study treatment in Study 16349 Part A. Patients were similarly distributed among indolent and aggressive cohorts with respect to gender (50% female), median age (68 years, range 22-90) and were heavily pretreated (median number of prior anti-lymphoma therapies: 3, range 1-10). Other characteristics included B symptoms in 20% (12.1% in indolent and 25.6% in aggressive NHL). The following entities were represented: follicular (FL; n=16); CLL (n=13); small cell (SLL; n=1); marginal zone (MZL; n=3); DLBCL (n=15); mantle cell (MCL; n=11); transformed FL (n=6); peripheral T-cell, no other symptoms (PTCL, NOS; n=5); mediastinal large B-cell (MLBCL; n=1); anaplastic large cell lymphoma (ALCL; n=2); angioimmunoblastic T-cell lymphoma (AITL; n=2); and follicular Grade 3b (n=1). 48.7% of patients were refractory to rituximab, and 15.8% were refractory to bendamustine.

Table 3–1 Preliminary Efficacy Results Study 16349 Part A (Full Analysis Set, N=76; Independent Review Assessment)

	FL (n=16)	SLL (n=1)	CLL (n=13)	DLBCL (n=15)	MCL (n=11)	Trans formed (n=6)	PTCL, NOS (n=5)	MLBCL (n=1)	FL Gr 3b (n=1)	MZL (n=3)	ALCL (n=2)	AITL (n=2)
CR/CRu	3	0	0	0	2	0	1	0	0	0	0	1
PR	3	1	5	1	4	2	0	0	0	2	0	0
SD	7	0	6	6	0	0	1	0	0	1	1	0
PD	0	0	1	4	2	3	2	1	0	0	0	0
NE/NA	3	0	1	4	3	1	1	0	1	0	1	1

ALCL = anaplastic large cell lymphoma; AITL = angioimmunoblastic T-cell lymphoma; CLL= chronic lymphocytic leukemia; CR =complete response; CRu = CR unconfirmed; DLBCL= diffuse large B-cell lymphoma; FL = follicular lymphoma; Gr = grade; MCL = mantle cell lymphoma; MLBCL = mediastinal large B cell lymphoma; MZL = marginal zone lymphoma; NE = not evaluable by Investigator / Oncologist. NA = not available; PD =progressive disease; PR =partial response; PTCL = peripheral T-cell lymphoma; SD = stable disease; SLL = small cell lymphoma. Patients who have no post baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated were considered evaluable.
Source: IB for copanlisib (version 7.0, dated 23 APR 2015).

Limited number of patients (ie, nine) have so far been treated with Copanlisib at 30 mg (0.4 mg/kg). Of the 9 pts at 0.4 mg/kg dose level, n=3 were non-diabetics and n=6 diabetics. 30% of these patients had recorded Gr.1/2 hyperglycemia after copanlisib administration. This limited data suggest some target inhibition at 0.4 mg/kg (30 mg flat dosing).

Further details can be found in the IB for copanlisib, which contains comprehensive information on the test drug.

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 NRG Statistics and Data Management Center-Pittsburgh Office: 412-624-2666.

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 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow-up.

3.1.2 Women of child-bearing potential (WOCBP) must agree to use adequate contraception when sexually active. Patients should continue contraception for 6 months after finishing study drug. See Section 3.2.19.

3.1.3 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. (See sections 3.2.2, 4.11, 8.2.1, and 10.2 for details.) **(01/09/2017)**

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 recurrent or persistent endometrial cancer (endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma or adenocarcinoma not otherwise specified [NOS]). Histologic confirmation of the primary tumor is required. Pathology slides will be reviewed retrospectively, semiannually by the NRG Pathology Committee per the standard NRG Central Pathology Review schedule.

3.2.2 All patients must have a somatic PIK3CA gene mutation (i.e., R88Q in exon 1, N345K in exon 4, C420R in exon 7, E542K, E545X [E545A, E545D, E545G, and E545K], Q546X [Q546E, Q546K, Q546L, and Q546R] in exon 9, and M1043I, H1047X [H1047L, H1047R, and H1047Y], or G1049R in exon 20) in a representative primary or metastatic tumor sample confirmed by the Roche COBAS® PIK3CA Mutation Test at Q^2 Solutions. (See sections 4.1.1, 5.6, 8.2.1, and 10.2 for additional details.) (See section 8.1.2, "Screening Lab Kits" for information on ordering kits for mutation screening.) **(01/09/2017)**

3.2.3 All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.2.4 Patients must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1. Tumors within a previously irradiated field will be designated as 'non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.2.5 Prior Therapy:

- Patients must have recovered from effects of recent surgery, radiotherapy, or chemotherapy. At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: laparotomy, laparoscopy). There is no delay required for minor

procedures (e.g., tumor FNA or core biopsy, venous access device placement).

- Patients may have received prior radiation therapy for treatment of endometrial cancer. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para-aortic radiation therapy, intravaginal brachytherapy and/or palliative radiation therapy. All radiation therapy must be completed at least 4 weeks prior to registration.
- Patients may have received prior hormonal therapy for treatment of endometrial carcinoma. All hormonal therapy must be discontinued at least 4 weeks prior to registration.
- Patients may have received prior therapy (including chemotherapy, biologic/targeted therapy and immunotherapy) for treatment of endometrial cancer. All therapy must be discontinued at least 4 weeks prior to registration. Any investigational agent must be discontinued at least 30 days prior to registration.
- Patients must have had at least one prior chemotherapeutic regimen for management of endometrial carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.
    - Patients are allowed to receive, but not required to receive, up to a total of 3 lines of chemotherapy.

3.2.6 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination within 28 days prior to registration;
- Imaging of target lesion(s) within 28 days prior to registration;
- Completion of pre-study protocol specific assessments as required in 4.1.2.

3.2.7 Age ≥ 18

3.2.8 The trial is open to females only

3.2.9 Performance Status [ECOG/Karnofsky] of 0, 1 or 2 within 28 days prior to registration (see Appendix I).

3.2.10 Adequate hematologic function within 14 days prior to registration defined as follows:

- ANC ≥ 1,500/mcl
- Platelets ≥ 75,000/mcl
- Hgb ≥ 8 g/dL

3.2.11 Adequate renal function defined as follows:

- Creatinine ≤ 1.5 x ULN

3.2.12 Adequate hepatic function defined as follows:

- Bilirubin ≤ 1.5 x ULN (≤ 3 x ULN for patients with Gilbert syndrome)
  Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN

3.2.13 Cardiac Function:

- Left Ventricular Ejection Fraction (LVEF) ≥ 50%

3.2.14 Fasting cholesterol less than or equal to 300 mg/dl; fasting triglycerides less than or equal to 300 mg/dl.

3.2.15 PT such that international normalized ratio (INR) is less than or equal to 1.5 x ULN (or an in range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin) and a PTT less than or equal to 1.5 times the upper limit of normal.

3.2.16 The patient must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2.17 Diabetic patients (Type I or II diabetes mellitus) must have baseline HbA1c levels NOT higher than 8.5% at study entry.

3.2.18 Patients with hypertension on medical management must have systolic blood pressure < 150 mmHG or diastolic pressure < 90 mmHG at study entry.

NOTE: **-ULN is institutional or laboratory upper limit of normal**
-Please see the required timing of pre-treatment assessments in Section 4.1.2.

3.2.19 Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 28 days of registration.

The patient and her sexual partner(s) must agree to use adequate contraception when sexually active for the duration of the study and for 6 months after finishing study drug.

A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range maybe used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

3.3 Ineligibility Criteria

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

3.3.1 Patients who have had prior therapy with any PI3K/AKT/mTor pathway inhibitor.

3.3.2 Patients who have the following histologies: mucinous, squamous, sarcomas, carcinosarcomas, clear cell.

3.3.3 Severe, active co-morbidity defined as follows:

- Congestive heart failure > New York Heart Association (NYHA) class II (see Appendix II)
- Myocardial infarction or unstable angina less than 6 months before registration.

- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before registration. **(01/09/2017)**
- Non-healing wound, ulcer or bone fracture.
- Active, clinically serious infections > CTCAE Grade 2
- History of, or current autoimmune disease
- HIV infection (treatment involved in this protocol may be significantly immunosuppressive and protease inhibitors used in HIV+ patients are substrates and potent inhibitors or inducers of the cytochrome P450). Accordingly, co-administration with copanlisib may result in either drug accumulation and possible toxicity, or decreased efficacy.
- Hepatitis B (HBV) or hepatitis C (HCV). All patients must be screened for HBV and HCV within 28 days prior to registration using the routine hepatitis virus laboratorial panel. PI3K-AKT-mTOR pathway inhibitors are known to be immune-suppressants and increase the risk of infection in patients with advanced solid tumors. Protease inhibitors are a class of antiviral drugs that are widely used to treat HIV/AIDS and hepatitis caused by hepatitis C virus. These agents are substrates and potent inhibitors or inducers of the cytochrome P450 (CYP) and co-administration with copanlisib may result in either drug accumulation and possible toxicity, or decreased efficacy. For the above reasons patients with active HBV or hepatitis C infection are not eligible for enrollment. Patients with serologic markers of HBV immunization due to known vaccination (HBsAg negative, anti-HBc negative and anti-HBs positive) will be eligible.
- Previous or concurrent history of malignancies within 5 years prior to study treatment except for curatively treated:
    - Cervical carcinoma in situ
    - Non-melanoma skin cancer
    - Superficial bladder cancer (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor invades lamina propria])
- Patients with seizure disorder requiring medication. Seizure disorder medications are substrates and potent inducers or inhibitors of the cytochrome P450 (CYP) and co-administration with copanlisib may result in either drug accumulation and possible toxicity, or decreased efficacy.
- Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to registration.
- Proteinuria of CTCAE Grade 3 or higher (estimated by urine protein: creatinine ratio ≥ 3.5 on a random urine sample). Patients who recently (i.e., at least 30 days prior to registration) discontinued an anti-angiogenic therapy which caused proteinuria (ie, Grade 2 (> 2 to > 3 g of protein or 1-3.5 g/24 h) or grade 3 proteinuria (> 4 of protein or > 3.5 g/24 h) are not eligible for enrollment until proteinuria improves to < 2 g of protein per 24 h.
- History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator)
- Concurrent diagnosis of pheochromocytoma.
- Unresolved toxicity higher than CTCAE Grade 1 attributed to any prior therapy/procedure, excluding alopecia.
- Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation (See Section 9.1.3).

3.3.4 Prohibited Therapies

- Strong CYP3A4 inhibitors and inducers (see Appendix V). Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted within two weeks prior to start of study treatment and for the duration of treatment with copanlisib.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor), Seville oranges and star fruit consumption is not permitted during the study.
- Anti-arrhythmic therapy other than beta blockers or digoxin.
- Systemic continuous corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not allowed. Patients may be using topical or inhaled corticosteroids.
- Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies.
- Concomitant radiotherapy.

3.3.5 Women who are breast feeding.

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

4.1 PRE-TREATMENT ASSESSMENTS

4.1.1 SCREENING (01/09/2017)

Assessments	
Confirmation of a somatic PIK3CA gene mutation[1] in a representative primary or metastatic tumor sample by Roche COBAS® PIK3CA Mutation Test at Q[2] Solutions[2]	Screening Consent and Screening Registration Required Prior to Testing

1. R88Q in exon 1, N345K in exon 4, C420R in exon 7, E542K, E545X (E545A, E545D, E545G, and E545K), Q546X (Q546E, Q546K, Q546L, and Q546R) in exon 9, and M1043I, H1047X (H1047L, H1047R, and H1047Y), or G1049R in exon 20
2. Six unstained formalin-fixed, paraffin-embedded (FFPE) sections (charged, 5µm) of primary or metastatic tumor are required for testing. Sections must contain at least 30% tumor. Tumor must be obtained by surgery or biopsy only (i.e., bone metastases, FNA, and cell blocks are not acceptable). Testing kits will be provided by Q[2] Solutions. *Note: Testing kits are typically received 7-10 business days after request. Typical testing turnaround time is five business days upon receipt of the sample.* (See sections 3.2.2, 5.6, 8.1.2, 8.2.1, and 10.2 for details.)
3. The NRG-GY008 Documentation page of the NRG Oncology website: https://www.nrgoncology.org/Protocol-Documents/NRG-GY008 contains the most recent information on pre-treatment assessments including the Q2 Solutions shipping address, pre-screening instructions and lab report upload form. If you have any additional questions, please contact NRG Support (support@nrgoncology.org). **(05/01/2017)**

4.1.2 PRE-TREATMENT

Assessments	Prior to Registration (calendar days)	Prior to Treatment (Cycle 1, Day 1) (calendar days)
History and Physical	≤ 28 days	≤ 28 days
Vital Signs (Temperature, Pulse Rate, Respiration Rate, Blood Pressure)	≤ 28 days	Day of treatment
Performance Status	≤ 28 days	≤ 28 days
Toxicity Assessment	≤ 14 days	≤ 14 days
Concurrent Medications	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Electrolytes, BUN, creatinine, Ca, magnesium, albumin and glucose	≤ 14 days	≤ 14 days
Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin	≤ 14 days	≤ 14 days
Urine Protein **(05/01/2017)**	≤ 14 days	≤ 14 days
HbA1c (for Diabetic patients)	≤ 14 days	≤ 14 days
Cholesterol/Triglycerides (fasting)	≤ 28 days	≤ 28 days
PT-INR/PTT	≤ 14 days	≤ 14 days
Hepatitis panel, including hepatitis B surface antigen and hepatitis C Antibody	≤ 28 days	≤ 28 days
Pregnancy Test (if childbearing potential exists)	≤ 28 days	≤ 7 days
ECG	≤ 28 days	≤ 28 days
LVEF[2]	≤ 28 days	≤ 28 days
Radiographic Tumor Measurement[1]	≤ 28 days	≤ 28 days

1. Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality.
2. Bayer will cover the cost of the LVEF test.

4.2 ASSESSMENTS DURING TREATMENT

Assessments	Cycle 1, Day 1	Cycle 2 and subsequent Cycles, Day 1	All Cycles, Days 8 and 15
History and Physical	X	≤ 3 days of treatment	
Vital Signs (Temperature, Pulse Rate, Respiration Rate, Blood Pressure)	X	X	X
Performance Status	X	≤ 3 days of treatment	
Toxicity Assessment[6]	X	≤ 3 days of treatment	X
Concurrent Medications	X	≤ 3 days of treatment	
CBC/Differential/Platelets	Weekly during Cycle 1	≤ 3 days of treatment	≤ 1 day of treatment for the first cycle and as clinically indicated thereafter
Electrolytes, BUN, creatinine, Ca, magnesium, albumin	X	≤ 3 days of treatment	
Bilirubin, ALT, AST, Alkaline Phosphatase	X	≤ 3 days of treatment	
Cholesterol/Triglycerides (fasting)	X	≤ 3 days of treatment (every 3 cycles, e.g., Cycle 3, 6, 9, ect)	
Glucose	1	2	1, 2
Blood Pressure	3	4	4
Radiographic tumor measurement	5		

1. Pre-dose glucose should be taken after 8 hours of fasting. For Cycle 1, glucose should be measured at pre-dose, 1 hour and 2 hours, after the start of copanlisib infusion. Please see Section 5.1.2 for additional information regarding pre-dose glucose for cycle 2 and beyond.
2. For Cycle 2 and subsequent infusions, glucose should be measured prior to and 1 hour after the start of copanlisib infusion. See Section 5.1.2 for fasting requirements.
3. For Cycle 1, Day 1: measure blood pressure pre-dose, 30 minutes after starting dose, at end of infusion, and 2 and 3 hours after completing infusion. For Cycle 1, Days 8 and 15: measure blood pressure pre-dose, 30 minutes after starting dose and at end of infusion.
4. For Cycle 2 and subsequent infusions, measure blood pressure pre-dose, 30 minutes after starting dose and at end of infusion.

NOTE: For all timepoints (glucose and blood pressure) a window of +/- 10 minutes is permitted

5. Radiographic tumor measurements to follow lesion for measurable disease every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) for the first 12 months; then every 12 weeks (+/- 7 days) thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. An excel tool is provided to calculate dates of re-imaging.
6. Report all adverse events that occur within 30 days of last protocol treatment on the Toxicity form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 7.

4.3 ASSESSMENTS IN FOLLOW-UP

Assessments	From end of protocol treatment: q3 mos. x 2 yrs.; q6 mos. x 3 years[1]
Vital Status	X
Toxicity Assessment[2]	X
LVEF	3
Radiographic tumor measurement[4]	X

1. Follow-up forms are collected for the 5-year follow-up period or until study termination. See Section 5.10 for further information.
2. Patients who discontinue treatment for unacceptable adverse events(s) will be followed until resolution of stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.
3. LVEF to be completed at end of treatment. Bayer will cover the cost of the LVEF test.
4. Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to re-assess disease using the same modality as for pre-treatment baseline imagine (see Section 4.1), until disease progression is confirmed according to guidelines in section 4.2.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

The treatment plan consists of weekly copanlisib for the first 3 weeks of a 28-day cycle (on Days 1, 8 and 15), followed by a 1-week break (i.e., no infusion on Day 22) **(01/09/2017)**

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

5.1.1 Protocol-Directed Therapy

Copanlisib 60 mg IV over 1 hour weekly, 3 weeks on/1 week off (i.e., Days 1, 8 and 15 of a 28-day cycle) until disease progression or adverse effects prohibit further treatment.

Study drug is administered in a normal saline solution, intravenously, over 1 hour. **No intravenous glucose preparations should be administered on the days of infusion.**

No dose should be given if blood pressure is greater than or equal to 150/90 mmHg (See Section 6.6.2).

5.1.2 Requirements for fasting state and pre-dose glucose levels

Fasting Requirements and Pre-dose Glucose levels			
Period	Fasting ≥ 8 h required before first glucose measurement	Pre-dose glucose levels	Fasting required before study drug infusion
Day 1 of Cycle 1	Yes	≤ 125 mg/dL (non-diabetic patients) < 160 mg/dL (diabetic patients)	Yes
Day 1 of Subsequent Cycles	Yes	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting)[a]	Conditional[b]
Days 8 and 15 of each Cycle	No	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting)	Conditional[b]

[a] In case of non-compliance with the fasting requirement.

[b] The conditional decision regarding meal timing and fasting will be made on Cycle 1 Day 8, based on the glucose response patterns of meal timing during Cycle 1 Day 1. This decision will be applied to subsequent infusion days (see text below "Recommendations of meal timing on infusion days" for further details).

The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site and will also document the timing of any caloric intake (meal, snack, Juice, etc). Fasting for this purpose refers to a ≥ 8 hour fast. Non-fasting status includes any caloric intake such as meals and also juice, snacks, and other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood, using a hand-held glucose meter. Any capillary blood (using hand-held glucose meter) glucose of > 250 mg/dL should be repeated via laboratory analysis.

5.1.2.1 Recommendations on meal timing on infusion days

The investigator will review the glucose profile during and post the copanlisib infusion of C1D1).

C1D1:

On C1D1 a low glycemic index meal (see Appendix III) may be taken 3 hours after the start of the study drug infusion.

C1D8:

The following recommendations apply to subsequent infusion days starting from C1D8:

If the maximum glucose during C1D1 was:

- < 200 mg/dL, the patient may have a low glycemic index meal or snack before, during or after the study drug infusion.

If the maximum glucose during C1D1 was

- ≥ 200 mg/dL, a low glycemic index meal can be taken 3 hours after the start of the study drug infusion (approximately 2 hours after the study drug infusion is completed).

The investigator should consider the administration of oral glucose lowering medication on C1D8 and subsequent infusion days of copanlisib. See Section 6.6.3 for additional guidance on glucose management.

5.1.3 Dosing criteria

On Day 1 of each subsequent cycle, the dose of study treatment will be given only if the criteria described in the table below are met. Glucose lowering medication can be used to optimize pre-infusion glucoses (see Section 6.6.3).

Laboratory test criteria for Day 1 dose of SUBSEQUENT cycles	
Laboratory Test	Criteria for Day 1 dose
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL[a]
ANC	≥ 1,500/mm^3
Platelets	≥ 75,000/mm^3
ALT	≤ 3 x ULN
AST	≤ 3 x ULN
Total bilirubin	≤ 1.5 x ULN [b]
Creatinine	≤ 1.5 x ULN

a: If hemoglobin is < 8g/dL on the day of planned study drug administration patient must be transfused to reach an Hb ≧ 8g/dL to continue on study treatment. Rationale and treatment should be recorded in source document and eCRF.

b: ≤ 3 x ULN in patients with Gilbert syndrome

A blood count and glucose will be performed and assessed prior to study drug infusion on Day 8 and 15 of the first cycle and as clinically indicated thereafter. On Days 8 and 15, the dose of copanlisib will be administered if, on the day of scheduled dosing, the laboratory test criteria for hemoglobin, ANC, platelets and glucose described in the table above are met. A delay >21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment. A patient will be permitted to have a new cycle of therapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

It will be acceptable for "Day 8 chemotherapy" to be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" to be given on Day 14, Day 15, or Day 16. A delay of more than this

one day window will be considered a missed dose. Missed doses will not be replaced. **The minimum interval needed between two infusions of study drug is 5 days.**

5.2 Radiation Therapy
Not Applicable.

5.3 Surgery
Not Applicable.

5.4 Device
Not Applicable**.**

5.5 Imaging (for imaging-focused study)
Not Applicable.

5.6 Integral Assay/Biomarker (01/09/2017)
The COBAS® PIK3CA mutation test is a real-time PCR test for the qualitative detection and identification of mutations in exons 1, 4, 7, 9, and 20 in the PIK3CA gene. This assay has been validated for the analysis of clinical samples in various solid tumor tissues and is performed per Q^2 Solutions Standard Operating Procedures (SOPs). Additional qualification on endometrial carcinoma tissue may be required.

All molecular analyses at Q^2 Solutions are done in compliance with College of American Pathologists (CAP) requirements for molecular testing and in accordance with Clinical Laboratory Improvement Amendments (CLIA) and Good Clinical Laboratory Practice (GCLP) guidelines. Validation report and SOPs are available upon request.

As part of Q^2 Solutions standard quality control measures for somatic mutation analysis from FFPE tissue, all samples will undergo H&E assessment by a board-certified pathologist prior to testing. This will ensure the specimen contains sufficient tissue area and the minimum tumor percentage (≥10%) required for testing. If less than 10% tumor nuclei are present, the sample will undergo macrodissection to enrich for tumor content. If sufficient material cannot be obtained from a single section, additional sections may be used.

Note: Testing kits are typically received 7-10 business days after request. Typical testing turnaround time is five business days upon receipt of the sample.

Any remaining slides or extracted DNA will be stored at Q^2 Solutions until returned to the NRG BB-Columbus for future (approved) research projects.

5.7 Intervention Not Otherwise Categorized
Not Applicable.

5.8 General Concomitant Medication and Supportive Care Guidelines

5.8.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Standard therapies for concurrent medical conditions
- Treatment with non-conventional therapies including herbs, vitamins, and other over-the-counter medications can interfere with copanlisib metabolism. Consult the study investigator prior to use.
- Bisphosphonates
- Patients who are therapeutically treated with an agent such as warfarin or low molecular weight heparin will be allowed to participate provided that their medication dose and INR/PTT is stable. Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until it is stable.
- Antiemetics: Anti-emetics may be administered according to standard practice upon identification of symptoms requiring intervention. The use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed to manage symptoms.
- The use of corticosteroids as antiemetics prior to copanlisib administration is not allowed.
- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial.
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin or low molecular weight heparin are permitted.
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin.
- Therapeutic drugs known to be substrates of P-gp and/or BCRP with narrow therapeutic index should be used with caution and patients monitored for any sign of toxicity. Furthermore, sensitive substrates of the renal drug transporter MATE2K (e.g. metformin) need to be used with caution (see Appendix IV). Calcium channel blockers may be used to control pre-existing hypertension. Non-dihydropyridine calcium channel blockers (Verapamil and diltiazem) should be avoided due to a potential CYP3A4 interaction (See Appendix V).
- Short term (up to 7 days) systemic corticosteroids above 15 mg prednisone or equivalent will be allowed only for the management of acute conditions.

5.8.2 Prohibited Therapies

- CYP3A4 inhibitors and inducers (see Appendix V). Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted within two weeks prior to start of study treatment and for the duration of treatment with copanlisib.

- Grapefruit and grapefruit juice (CYP3A4 inhibitor), Seville oranges and star fruit consumption is not permitted during the study.
- Anti-arrhythmic therapy other than beta blockers or digoxin.
- Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies.
- Concomitant radiotherapy.
- Systemic continuous corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not allowed. Patients may be using topical or inhaled corticosteroids.

5.8.3 Participation in Other Trials
Not applicable.

5.9 Duration of Therapy
In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:
- Disease progression,
- 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.
- Non-compliance to protocol

5.10 Duration of Study
All patients will be treated (with completion of all required case report forms) until disease progression or study treatment withdrawal. Thereafter, patients will be monitored for delayed toxicity and survival with follow-up forms for no more than 5 years or until study termination, unless consent is withdrawn.

A patient is considered off study therapy when the patient has progressed or died, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Report all treatment received on treatment reporting forms and adverse events on adverse event forms up until the patient qualifies as being off study therapy.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Dose modification
It is recognized that attribution of causality of any AE to the test drug specifically may be difficult. However, in Phase I and II trials, certain toxicities were seen only in relation to copanlisib (e.g., transient increases in glucose and blood pressure). Based on this knowledge the investigator may decide on the necessary dose modifications.

Dose modifications and treatment interruptions for copanlisib must be done according to the guidelines in Hematological toxicity and nonhematological toxicity sections.

The dose modification levels of copanlisib are:

Dose levels of Copanlisib	
Dose Level 1 (starting dose)	60 mg
Dose Level -1	45 mg
Dose Level -2	30 mg

Patients who do not tolerate the copanlisib dose of 30 mg must discontinue study treatment permanently.

6.2 Hematological toxicity

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events.

Dose Modification of Copanlisib for hematological toxicity			
Review laboratory test criteria for Day 1 dose of Subsequent Cycles (Section 5.1.3) Febrile neutropenia [a] INR or PTT CTCAE Grade 3 or greater with bleeding [b]		For platelets and ANC delay infusion until criteria displayed in the table in Section 5.1.3, "Laboratory test criteria for Day 1 dose of Subsequent cycles" are met.	
Grade 3	1st appearance	Delay until Grade ≤ 2	No change
	2nd appearance	Delay until Grade ≤ 2	Decrease by one dose level[c]
	3rd appearance	Delay until Grade ≤ 2	Decrease by one dose level[c]
	4th appearance	Permanently discontinue copanlisib	
Grade 4		Permanently discontinue copanlisib	

a: These patients should recover from neutropenia, without fever

b: INR and PTT should have returned to ≤1.5 x ULN with no signs of bleeding

c: Not applicable for 30 mg dose level

A delay >21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment. Copanlisib must be discontinued if the lowest dose level of 30 mg is not tolerated.

6.3 Non-hematological toxicity

Dose modifications for non-hematologic toxicities attributable to copanlisib except glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases are outlined in the table below:

Dose modification of copanlisib for non-hematological toxicity (except hyperglycemia, dermatologic toxicity, non-infectious pneumonitis and hypertension)			
Toxicity[a]	Occurrence	For Current cycle of therapy	For next cycle of therapy
Grade 1-2	Any appearance	No change	No change
Grade 3[b]	1st appearance	Delay until Grade ≤ 2	No change
	2nd appearance	Delay until Grade ≤ 2	Decrease by one dose level[c]
	3rd appearance	Delay until Grade ≤ 2	Decrease by one dose level[c]
	4th appearance	Permanently discontinue copanlisib	
Grade 4		Permanently discontinue copanlisib	

a: Toxicities according to CTCAE version 4.0
b: Despite maximum supportive therapy
c: Not applicable for 30 mg dose level

A delay >21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment. Copanlisib must be discontinued if the lowest dose level of 30 mg is not tolerated.

6.4 Dermatologic toxicity

The guidelines for dose modifications in cases of dermatologic toxicity are outlined in the table below.

Dose Modification of copanlisib for dermatologic toxicity			
Toxicity[a]	Occurrence	For current cycle of therapy	For next cycle of therapy
Grade 1	Any appearance	No change	No change
Grade 2[b]	1st appearance	Interruption until Grade ≤ 1	No change
	2nd appearance	Interruption until Grade ≤ 1	Decrease by one dose level [c]
	3rd appearance	Interruption until Grade ≤ 1	Decrease by one dose level [c]
	4th appearance	Permanent discontinuation	
Grade 3[b]	1st appearance	Interruption until Grade ≤ 1	Decrease by one dose level [c]

	2nd appearance	Interruption until Grade ≤ 1	Decrease by one dose level [c]
	3rd appearance	Permanent discontinuation	
Grade 4	1st appearance	Permanent discontinuation	

a Toxicities according to CTCAE version 4.0
b Despite maximum supportive therapy
c Not applicable for 30 mg dose level

The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level study drug and meets criteria for further decrease of dose, study drug will be discontinued permanently.

6.5 Non-infectious pneumonitis (NIP)

In the event of suspected NIP of any grade, copanlisib must be interrupted. If NIP is the final diagnosis, copanlisib must be permanently discontinued. Pneumonitis is to be reported as such only in the event of NIP. Study Chair notification in the event of any grade NIP is required.

The investigator is requested to differentiate between non-infectious pneumonitis (NIP), and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion, and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

6.6 Glucose increases and blood pressure increases

6.6.1 Glucose increases

Patients who develop transient post-infusion glucose > 250 mg/dL after copanlisib administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting). Glucose levels >250 mg/dL should be confirmed by repeated laboratory analysis. Guidelines for the treatment of glucose increases are given in Section 6.6.3.

A dose reduction of copanlisib by one dose level is mandatory in the event of hyperglycemia > 500 mg/dL (repeated immediately and confirmed by laboratory glucose test) or in the event of persistent CTCAE Grade ≥ 3 glucose (persistent > 250 mg/dL value confirmed by repeated laboratory analysis) despite optimal glucose lowering therapy. Treatment will be permanently discontinued if persistent CTCAE Grade ≥ 3 glucose occurs at 30 mg dose level despite optimal glucose lowering therapy.

6.6.2 Blood pressure increases

No dose should be given if blood pressure is ≥ 150/90 mmHg. Instructions for blood pressure measurement are given in the table below. Antihypertensive medication may be given to control the hypertension. Dosing can proceed on the scheduled day if there are at least 2

consecutive measurements <150/90 mmHg. Otherwise dosing must be delayed.

The guidelines for dose modifications of study treatment in case of increased blood pressure are given in the table below.

Dose modification of study treatment for increases of blood pressure		
Toxicity	Study Drug action	Recommendation
Pre-dose measurements BP ≥ 150/90 mmHG	No dose should be given until recovery to < 150/90 mmHg	Consider administering BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to < 150/90 mmHG. If BP does not return to < 150/90 mmHG then delay dosing until next visit.
During infusion: BP ≥ 160/100 mmHG (or CTCAE Grade ≥ 3)	Infusion can be interrupted or slowed down and administration of anti-hypertensive therapy should be initiated.	Infusion may be resumed immediately when BP has returned to < 150/90 mmHg or skipped. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion[b]
Post-dose: BP ≥ 160/100 mmHG[a]	_____	Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion
Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated(CTCAE Grade 4)	Permanent Discontinuation	_____

a: Not manageable despite optimal hypertensive treatment

b: The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and experiences post-dose increase BP of ≥ 160/100 mmHg, consider more intensive therapy than previously used.

Treatment of blood pressure increases associated with copanlisib
It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule, and take their usual doses on the days of study drug infusion. The management of acute blood pressure increases following copanlisib will need to be individualized for each patient, but the experience in Phase I has suggested the benefit of dihydropyridine calcium channel blockers (i.e., amlodipine, felodipine). Topical nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers) should be avoided due to a potential CYP 3A4 interaction.

In general, it is advisable for sites to be prepared, so that antihypertensive medication is readily available in case of need.

6.6.3 Management of glucose increases that can occur with copanlisib

6.6.3.1 Management of transient post-infusion glucose increases in non-diabetic patients

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially.

6.6.3.2 Asymptomatic transient glucose increases

- Blood glucose ≤ 250 mg/dL. Does not generally require treatment with glucose lowering medication.
- Blood glucose > 250 mg/dL. Should have repeated laboratory glucose determination. If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication if hydration status is normal as clinically assessed.

6.6.3.3 Symptomatic or persisting glucose increases

- Symptomatic glucose increase of any grade. Hydration status should be clinically assessed. If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV).
- Blood glucose > 250 mg/dL. Should have repeated laboratory glucose determination. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicate the need for hydration, glucose lowering medication should be administered.

6.6.3.4 Glucose lowering medication

During the same infusion day as increased glucose is identified:

- Rapid or short acting (or Regular) insulin may be given for glucose levels that are persisting at > 250 mg/dL, or if the patient is symptomatic during the infusion day.
- "Sliding scale" or short acting (or Regular) insulin coverage of glucose levels that are persisting at > 250 mg/dL is recommended, with oral or IV hydration as clinically appropriate.

During the subsequent infusions:

Administration of oral glucose lowering medication that will cover meals on the subsequent infusion day(s) is recommended. Recommended oral glucose lowering medications include use of either a morning dose of sodium/glucose co-transporter 2 (SGLT2) inhibitor or dipeptidyl peptidase-4 (DPP4) inhibitor. Please refer to local prescribing information on oral glucose lowering medications (consider endocrinology consult for guidance). The use of sulphonylurea/metaglinide medications to manage increased glucose levels post copanlisib infusions is not recommended.

6.6.3.5 Persisting glucose > 250 mg/dL that does not promptly improve with insulin/oral medication/clinically appropriate hydration:

- Prompt input from a diabetes specialist (endocrinologist) should be obtained.
- Consider hospitalization to stabilize the patient metabolically if intravenous

hydration is needed.

6.6.3.6 Management of post-infusion glucose increases in diabetic patients

Patients with diabetes mellitus (types 1 and 2) will require the input of a diabetes specialist (endocrinologist) to anticipate glucose lowering needs on study drug infusion days. Adjustment of the patient's glucose lowering regimen (whether adjustments to prior use of oral hypoglycemic medication, insulin, or a combination of both) with special attention to post-infusion meal coverage should be considered for post-prandial glucose increases.

Patients who have experienced glucose increases requiring supplemental glucose lowering medication on the infusion day, may benefit from glycemic observation and potential glucose lowering medication on days subsequent to the infusion day. These patients may be referred to a local diabetes specialist/endocrinologist for glucose management if appropriate. Alternatively, the investigator will be free to adequately manage these patients in the same way as indicated above.

6.6.3.7 Monitoring period continuation: infusion clinic visit days and during continued monitoring periods

All patients (diabetic and non-diabetic) should be kept under close observation if the glucose level is > 250 mg/dL until the non-fasting glucose level decreases to < 200 mg/dL at any cycle.

All diabetic patients, as well as non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion will be instructed to check blood glucose at home at least 3 times per full day for at least 72 hours after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further measurements approximately 2 hours after intake of food. If after the required 72 hours the glucose values are not at goal (non-fasting glucose < 200 mg/dL), this monitoring will continue until blood glucose values are at goal.

Patients will be trained how to measure their capillary blood glucose levels at home. If applicable, patients will be provided with glucose meter and supplies (lancets, test strips and diary) to register measured values and record oral glucose lowering medication and/or insulin administration. (See Section 9.2.)

In the event of rapid or short acting (Regular) insulin administration was administered on an infusion day at any cycle, a minimum 3-hour close observation time is required post insulin administration.

Low glycemic index meals should be advised for patients who are kept in the clinic in for continued observation (see Appendix III). A low glycemic index diet is recommended for the first 48 hours after study drug infusion. However, caloric restriction is not intended for the population under study.

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinic source documentation. See Appendix VIII.

6.6.3.8 Monitoring of diabetic patients

If the patient has known diabetes and already monitors her blood glucose as part of routine diabetes care, the routine measurements should not be replaced by the study-specific measurements. In this situation, patients should add the study-specific measurements to their routine, if applicable. After the required 72 hour post-infusion, if blood glucose values are at goal (non-fasting glucose < 200 mg/dL), patients can then stop only the study-specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.

6.6.4 Management of hyperlipidemia

As lipids are monitored for the duration of this study it is recommended to treat significant deviations from normal range with standard interventions and therapy in standard doses according to local medical practice. Significant deviations from normal range are defined as fasting cholesterol less than or equal to 300 mg/dl; fasting triglycerides less than or equal to 300 mg/dl (ie, eligibility criteria). In case of significant deviations the use of therapeutic life-style changes (TLC), fibrates (fenofibrate or gemfibrozil) or statin, will be recommended to sites per published algorithm (ie, Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway" (J Clin Oncol 30:2919-2928, 2012).

Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, these goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events).

6.6.5 Treatment of vomiting and diarrhea

The hydration status of the patient should be clinically assessed, with fluid replacement (oral or IV) as appropriate. Adequate hydration through appropriate fluid maintenance is essential in the treatment of diarrhea or vomiting. Anti-diarrhea medications may be introduced if symptoms occur.

The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours; a maximum daily dose of 16 mg is not to be exceeded. If clinically indicated, diphenoxylate hydrochloride with or without atropine sulfate can be used. The routine use of standard antiemetics, including 5-HT3 blockers is allowed, see permitted concomitant therapy section below. In the event of CTCAE Grade 3 diarrhea with maximal pharmacological support, the administration of the test drug should be delayed.

6.6.6 Treatment of dermatologic toxicity

If dermatologic changes occur, the patient should be treated quickly and aggressively.

Guidance on treatment of skin toxicities	
MILD (CTCAE Grade 1)	
Dry Skin/Fissures	Emollients, Eucerin or Aquaphor plus gentle soaps (Dove,

	Cetaphil, Basis), use fragrance-free detergents
Rash	Topical hydrocortisone 2.5% and/or clindamycin 1% gel plus doxycycline 100 mg BID or Minocyclin 100 mg BID
Nail Changes	Moisturizers
Pruritus	Pramoxine 1% cream of Sama Ultra Cream
MODERATE (CTCAE Grade 2)	
Dry Skin/Fissures	Emollients and topical as above plus Ammonium lactate or Ureas 20%
Rash	Topical hydrocortisone 2.5% and/or clindamycin 1% gel plus doxycycline 100 mg BID or Minocycline 100 mg BID
Nail Changes	Vinegar soaks (dilute 1:1 white vinegar in water and soak fingers for 10 minutes a day)
Pruritus	H1-anti-histamines
SEVERE (CTCAE Grade 3 or 4)	
Dry Skin/Fissures	As above for Moderate
Rash	As above for Moderate plus Medrol dose pack[a]
Nail Changes	Topical antibacterials/antifungals (ciclopirox) cream or Topical high potency steroids (closbetasol ointment) Consider dermatology consult for nail avulsion
Pruritus	Pregabalin 50-100 mg BID

a Cross check with short-term corticosteroid administration (see Exclusion Criteria and Permitted concomitant therapy)

If concomitant corticosteroids are used for dermatologic conditions, the investigator should be alert to potential impact of corticosteroids on increases in blood glucose and in blood pressure. Please refer to excluded previous therapies in Exclusion Criteria section. If glucose increases or blood pressure increases during the period of corticosteroid use, please see Section 6.6.3 for glucose management, and see Section 6.6.5 for blood pressure management.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY008, copanlisib, is being made available under an IND sponsored by NRG Oncology. For patients receiving copanlisib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.42 of the protocol. **(01/09/2017)**

7.2 Adverse Events and Serious Adverse Events

7.2.1 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.

7.2.2 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 Adverse Events for Investigational Study Agents Not Provided by CTEP

Refer to the copanlisib Investigator Brochure (IB). **(01/09/2017)**

7.4 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 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 the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 3 days.
- Supporting source documentation is requested by 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 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.

7.4.2 Expedited Reporting Requirements for Adverse Events

Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-CTEP 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 NRG via CTEP-AERS within 24 hours of learning of the AE, followed by a complete report within 3 calendar days of the initial 24-hour report.

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

[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 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs
- Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements:

Non-infectious pneumonitis (NIP)

Non-infectious pneumonitis (NIP) of any grade requires expedited reporting via CTEP-AERS. Pneumonitis is to be reported as such only in the event of NIP.

The investigator is requested to differentiate between non-infectious pneumonitis (NIP), and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion, and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

7.4.3 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.

7.4.4 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.

7.4.5 Reporting to the Pharmaceutical Company: The CTEP-AERS report will be sent directly to Bayer via the CTEP-AERS system upon submission to NCI.

7.4.6 Reporting to the FDA: The NRG Oncology Regulatory Department will submit an IND safety report to the FDA and all participating investigators no later than 15 calendar days after determining that the suspected adverse reaction or other information qualifies for reporting (21

CFR 312.32(c)(1)). Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the FDA no later than 7 calendar days after initial receipt of the information by GOG (21 CFR 312.32(c)(2). Each report will be submitted on FDA Form 3500A (21 CFR 320.31(d)(3)).

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>.

8.1.2 Requirements for NRG-GY008 Site Registration (01/09/2017) (05/01/2017)

Before patient enrollment, submit the following documents to the NRG Oncology Regulatory Department (See Section 8.1.2.2):

- CTSU Transmittal Sheet (optional)
- IRB approval letter (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 a combination is accepted)
- IRB-approved informed consent
- IRB Membership list or IRB assurance number
- FDA Form 1572 for institution PI (study-specific)
- Current CV (signed and dated within 2 years) for institution PI and all sub-investigators listed on FDA Form 1572
- Medical License for institution PI and sub-investigators listed on FDA Form 1572
- Lab license, certificates, and Normal Lab Values (NLV) for labs listed on FDA Form 1572
- Signed Investigator Signature Page
- Signed Financial Disclosure Form for all investigators listed on FDA Form 1572
- Pharmacy Information Form

Screening Lab Kits (01/09/2017)

Initial lab kit supplies must be ordered and all essential documents must be approved before a site can be activated to screen the first patient. NRG Oncology will order the initial kit supply based on information provided on the online GY008 Lab Kit Registration Form. The delivery of kits can take at least 3 weeks after the initial kit order is placed. After receipt of the initial kit supply, sites will be responsible for ordering all other biospecimen kits through the Q^2 Solutions Infosario™ website. Q^2 Solutions will email the site designee with information about accessing the Q^2 Solutions Infosario™ website.

The NRG Oncology Regulatory Department Administrative Office will receive, review, and approve all regulatory documents. **Please allow 7-10 days for review and approval of all documents prior to screening first patient.**

8.1.2.1 IRB Approval (01/09/2017)

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 separate 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. **(05/01/2017)**

8.1.2.2 Submitting Regulatory Documents:

The required regulatory documents can be submitted electronically or via mail to the NRG Oncology Regulatory Department.

NRG Oncology Regulatory Department
ATTN: NRG-GY008
1600 JFK Blvd., Suite 1020
Philadelphia, PA 19103
E-mail: NRG-GY-Regulatory@nrgoncology.org

8.1.2.3 Checking Your Site's Registration Status: (01/09/2017)

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.

8.2 Pre-registration Requirements

8.2.1 Screening for PI3KCA Mutation Status (01/09/2017)

Results of the Roche COBAS® PIK3CA Mutation Test (Q^2 Solutions) are required at the time of step two of patient enrollment.

Patient enrollment will be a two-step process in OPEN (See section 8.3.1). After the patient has signed the screening consent, step zero will initiate the patient in the enrollment process and assign a patient ID. Patients will have a representative primary or metastatic tumor sample screened for the PIK3CA mutation. Once the results of the PIK3CA mutation testing are provided to the site by Q^2 Solutions and the patient is known to meet the PIK3CA eligibility criterion, the report is uploaded to the NRG website to undergo internal review. Once the PIK3CA mutation is confirmed internally, step 1 of the process is completed. Step 1 further assesses all eligibility criteria. Please see the "NRG-GY008 Prescreening Instructions" document for additional information.

(See sections 3.2.2, 4.1.1, 8.2.1, and 10.2 for details.)

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).
- Confirmation of PI3CKA mutation (See sections 3.2.2, 5.6, and 10.2 for details.)

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: support@nrgoncology.org or call the NRG Registration Desk at 1-800-523-2917, 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.

9. DRUG AND DEVICE INFORMATION

9.1 Investigational Study Agent

Copanlisib (BAY 80-6946), NSC #784727, IND # 130822, IND Sponsor: NRG Oncology **(01/09/2017)**

9.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride, NSC 784727) (01/09/2017) (04/10/2017)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 425 patients.* Below is the CAEPR for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride).

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 2.1, January 21, 2017[1]

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 4.0 Term) [n= 425]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		***Musculoskeletal and connective tissue disorder - Other (muscle spasms) (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Paresthesia		

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 4.0 Term) [n= 425]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 2)***

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

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

[3]Pneumonitis is a group term that includes interstitial lung disease, dyspnea, dyspnea at rest, and dyspnea exertional.

Adverse events reported on copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (eosinophilia, including eosinophil count decreased)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Left ventricular systolic dysfunction; Myocardial infarction; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Dyspepsia; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Oral dysesthesia; Oral pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Fever; General disorders and administration site conditions - Other (failure to thrive); Infusion related reaction; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Ejection fraction decreased; Investigations - Other (blood insulin increased); Investigations - Other (electrocardiogram T wave abnormal); Lipase increased; Lymphocyte count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (psoriatic arthropathy); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea[3]; Hypoxia; Pleural effusion; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Pruritus; Rash acneiform; Stevens-Johnson syndrome
VASCULAR DISORDERS - Vascular disorders - Other (circulatory collapse)

Note: Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) 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.

9.1.2 Investigator Brochure

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure (IB) for comprehensive pharmacologic and safety information.

The IB can be requested by sending a request to NRG-GY-Regulatory@nrgoncology.org. In the subject line, please state, "NRG-GY008 IB Request". The following information must be stated in the request:

Institution Name
CTEP Institution Code
Principal Investigator

9.1.3 Availability/Supply **(01/09/2017)**

The following excipients are used to manufacture the medicinal product: mannitol, NaOH, and citric acid, and water for injection. The medicinal product is a freeze-dried product containing 60 mg of copanlisib (equivalent to 69.12 mg BAY 84-1236) in a 6 mL injection vial.

Copanlisib is supplied as a lyophilized preparation in a 6-mL injection vial. After reconstitution with 4.4 mL of sodium chloride, the drug substance concentration amounts to 15 mg/mL Copanlisib. The labeled amount per vial is 60 mg Copanlisib, the nominal content due to the technically required overfill is 68.4 mg Copanlisib per vial.

Copanlisib will be supplied by Bayer and distributed by Biologics, Inc.

9.1.4 Reconstitution:

Reconstitution medium for the lyophilisate:	0.9% sodium chloride solution for injection (4.4 mL)
Dilution medium for the reconstituted product:	0.9% sodium chloride solution for injection (100 mL)

Colorless infusion bags (translucent), empty or filled with 100 mL 0.9% NaCl solution, made of polyethylene (PE), polypropylene (PP), or ethylene vinyl acetate (EVA)

Colorless infusion tubes (translucent), made of polyethylene (PE), polypropylene (PP) or polyvinylchloride (PVC) (DEHP-free) or polyurethane (PU)

9.1.5 Handling: For the handling of the study medication the following principles have to be followed:

- Use of sterile disposable gloves and hand hygiene as recommended for current clinical practice.
- Disinfection of the septum of the injection stoppers using a swab with an appropriate disinfectant (e.g. based on ethanol or isopropanol) [applies to vials of Copanlisib and sodium chloride solution].
- To ensure product sterility the vial stopper must not be removed during handling.

9.1.6 Dosage Preparation: These instructions are for the preparation of doses 30, 45, and 60 mg Copanlisib in 100 mL 0.9% NaCl bags. If starting with an empty bag, inject 100 mL of 0.9% NaCl into the bag to ensure a volume of not less than 100 mL.

For reconstitution add 4.4 mL of sterile isotonic sodium chloride solution to the lyophilized mass of one vial, leading to solutions with a drug substance concentration of 15 mg/mL. The appropriate volume of the reconstituted solution corresponding to the intended dose (see table below) is then withdrawn from the vial and diluted to the administration volume of 100 mL using physiological saline solution.

Process

- Withdraw 4.4 mL of sterile isotonic chloride solution as reconstitution media by using a 5 mL **sterile** syringe

(Note: the dosing of the reconstituted lyophilisate may alternatively be performed by gravimetric means, provided the density of the reconstituted solution is taken into account: D20 4= 1.0222 g/mL)

- Inject the measured volume through the stopper into the 6 mL injection vials using a needle
- Shake the injection vial vigorously for 30 seconds, and then allow standing for 1 minute to let the bubbles rise to the surface
- Check if any undissolved substance is still seen. If yes, repeat the shaking and settling procedure. The reconstituted lyophilisate may only be diluted or withdrawn after the solution is clear
- Withdraw the required amount of the reconstituted lyophilisate with an unused sterile syringe:

Copanlisib dose [mg]	**30**	**45**	**60**
Volume of reconstituted Copanlisib solution to be withdrawn from the vial (ml)	2	3	4

- Connect the syringe to the 100 mL sodium chloride bag and transfer the required amount of the reconstituted lyophilisate into the bag
- Mix the dose well
- After administration the line is to be flushed to ensure patient gets the complete dose

First Aid Measure in Case of Accidental Skin Contact
Remove all contaminated clothes and shoes and wash off immediately with soap and plenty of

Water.

9.1.7 Storage and Shelf Life: The drug product has to be stored between +2ºC and +8ºC and should not be transported above +30ºC.
Stability of the diluted solution
The diluted solution is physically and chemically stable for 24 hours at room temperature. However, for microbiologic consideration, diluted solution should be stored between +2ºC and +8ºC if not administered immediately.

9.1.8 Drug Interactions Encountered in Clinical Trials: Preliminary analysis of Study 16270 showed that the ACU of copanlisib was increased by 1.53% when copanlisib was coadministered with itraconazole (a strong CYP3A4 inhibitor).

9.1.9 Agent Ordering and Agent Accountability

9.1.9.1 Drug Distribution: Following submission and approval of all required regulatory documents, the Pharmacy Information Form will be forwarded to Biologics notifying them that an institution has been approved to receive drug/supplies.

All study drug will be shipped with a protocol-specific label adhered to the outside of the packaging. Each protocol-specific label includes the following information:

- The Study Number (NRG-GY008)
- Drug Identification
- Lot # and Expiration Date
- Dosing instructions (Administer as directed per Protocol NRG-GY008)
- Storage instructions (Store at 2-8°C)
- Emergency contact instructions
- IND caution statement and/or local regulatory statements

All drug orders are shipped via *FedEx Priority Overnight* delivery for shipments to US sites. Study Drug is shipped in a Biologics branded package with appropriate materials to maintain temperature stability.

Institution Instruction upon Receipt of Study Drug: The designated site coordinator validates contents of package matches information provided on packing slip, signs off on the packing slip, and faxes completed form to Biologics at 919-256-0794 to validate shipment has been received and is accurate.

9.1.9.2 Initial Supply: Sites are permitted to request study drug for up to 5 patients for 1 cycle of treatment per order (total of 15 vials). To request drug, sites will need to submit a "Drug Order Request Form" to Biologics at 919-256-0794 or CRSorders@biologicsinc.com. **(05/01/2017)**

9.1.9.3 Subsequent Supply: If additional drug is needed, sites will need to submit a "Drug Order Request Form" to Biologics at 919-256-0794 or CRSorders@biologicsinc.com. **(05/01/2017)**

9.1.9.4 Drug Accountability: All study drug must be accounted for during the course of this study. Site must maintain an NCI Drug Accountability Record Form (DARF).

9.1.9.5 Drug Destruction: At the conclusion of the study, remaining inventory is documented on the DARF and unused drug is to be destroyed as per institution policy and recorded on the DARF. The final DARF must be forwarded to the NRG Oncology Regulatory Department via email to NRG-GY-Regulatory@nrgoncology.org.

9.2 Glucometers, Lancets and Glucometer Test Strips (05/01/2017)

Glucometers, lancets and glucometer test strips will be supplied and distributed by Biologics. Glucometers will be supplied in 1-ct boxes, lancets will be supplied in 100-ct boxes and glucometer test strips will be supplied in 25-ct boxes.

9.2.1 Glucometer and Glucometer Test Strip Distribution: Following submission and approval of all required regulatory documents, the Pharmacy Information Form will be forwarded to Biologics notifying them that an institution has been approved to receive glucometers, lancets and glucometer test strips.

The glucometers, lancets and glucometer test strips will be shipped with a protocol-specific label adhered to the outside of the packaging. Each protocol-specific label includes the following information: **(05/01/2017)**

- The Study Number (NRG-GY008)
- Device Identification
- Lot # and Expiration Date
- Device Instructions
- Storage instructions (Store at 15-30°C)
- Emergency contact instructions
- IND caution statement and/or local regulatory statements

All orders are shipped via *FedEx Priority Overnight* delivery for shipments to US sites and is shipped in a Biologics branded package with appropriate materials to maintain temperature stability.

Institution Instruction upon Receipt of Study Supplies: The designated site coordinator validates contents of package matches information provided on packing slip, signs off on the packing slip, and faxes completed form to Biologics at 919-256-0794 to validate shipment has been received and is accurate.

9.2.1.1 Initial Supply: One glucometer will be supplied to each patient enrolled. Biologics will ship up to 5 boxes of lancets, 5 glucometers, and 5 boxes of test strips per order (for up to 5 patients). Study supplies will be shipped in the original manufacturer's packaging. To request, sites will need to submit a "Drug Order Request Form" to Biologics at 919-256-0794 or CRSorders@biologicsinc.com. **(05/01/2017)**

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9.2.1.2 Subsequent Supply: If additional glucometer test strips are needed, sites will need to submit a "Drug Order Request Form" to Biologics at 919-256-0794 or CRSorders@biologicsinc.com. **(05/01/2017)**

9.2.1.3 Device Disposition: Sites are to follow institutional standard operations procedures for recycling or destroying the device.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Pathology Review Guidelines

Stained pathology slides from the primary diagnosis are required for retrospective review by the NRG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). Slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the NRG Statistics and Data Management Center-Buffalo Office individual slides must be labeled with NRG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the NRG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, and the official pathology report in your own shipping container using postal mail at your own expense directly to the **Pathology Materials Coordinator at the NRG Statistics and Data Management Center-Buffalo Office, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263; phone 716-845-5702.**

Retrospective Review

Patients must have recurrent or persistent endometrial cancer (endometrioid, serous, undifferentiated, mixed, and adenocarcinoma not otherwise specified [NOS] histologies are eligible). Patients with mucinous, squamous, or clear cell histologies, carcinosarcoma, or sarcoma are ineligible. Pathology slides will be reviewed retrospectively, semiannually by the NRG Pathology Committee, per the standard NRG Pathology Committee Central Review schedule.

10.2 Tissue Selection for Integral Marker Testing (01/09/2017)

Six unstained sections (charged, 5μm) of formalin-fixed, paraffin-embedded (FFPE) primary or metatstatic tumor is required for the COBAS® PIK3CA Mutation Test at Q^2 Solutions. Sections must contain at least 30% tumor. Tumor must be obtained by surgery or biopsy only (i.e., bone metastases, FNA, and cell blocks are not acceptable).

Note: Testing kits are typically received 7-10 business days after request. Typical testing turnaround time is five business days upon receipt of the sample.

(See sections 3.2.2, 4.1.1, 5.6, 8.1.2 and 8.2.1 for details.)

10.3 Tissue Selection for Integrated Marker Testing

FFPE primary or metatstatic tumor will be banked for retrospectively testing to evaluate PTEN status in all patients.

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.

10.4 Biospecimen Submission Tables

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

10.4.1 Mandatory Biospecimen Submissions (01/09/2017)

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 Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 15 unstained slides (10 charged, 5µm & 5 uncharged, 10µm)	Prior to all treatment	NRG Oncology Biospecimen Bank-Columbus within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 15 unstained slides (10 charged, 5µm & 5 uncharged, 10µm)	Prior to all treatment *(Optional if FP01 is submitted)*	

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

1 NRG BB-Columbus / Protocol NRG-GY008, 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

Not applicable.

10.5 Laboratory Testing

10.5.1 PTEN Mutation Testing (Integrated Biomarker)

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.

Pending subsequent review and approval of assay details in accordance with NCTN policies, formalin-fixed, paraffin-embedded (FFPE) tissue specimens will be retrospectively tested to evaluate PTEN status in all patients.

11. SPECIAL STUDIES (NON-TISSUE)

Not Applicable.

12. MODALITY REVIEWS

Not Applicable.

13. ASSESSMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [*Eur J Ca* 45:228-247, 2009] Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.1.1 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

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

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

13.1.2 Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal

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

NRG will not allow PET-CT use for RECIST 1.1 response criteria.

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

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

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

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

13.2 Response Criteria

Determination of response should take into consideration all target (See 13.2.1) and non-target lesions (See 13.2.2).

13.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (i.e. the nadir) while on study.

13.2.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.2.3 Evaluation of Best Overall (unconfirmed) Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions		New Lesions*	Time Point Response
CR	CR		No	CR
CR	Non-CR/Non-PD		No	PR
CR	NE		No	PR
PR	Non-PD or NE		No	PR
SD	Non-PD or NE		No	SD
NE	Non-PD		No	NE
PD	Any		Yes or No	PD
Any	PD**		Yes or No	PD
Any	Any		Yes	PD

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

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

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions		New Lesions*	Time Point Response
CR		No	CR
CR		No	Non-CR/non-PD*
Non-CR/non-PD		No	Non-CR/non-PD*
NE		No	NE
Unequivocal PD		Yes or No	PD
Any		Yes	PD

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

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.2.4 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	C
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	P
PR	PR	P
PR	SD	S
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

13.3 Duration of Response

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

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

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

13.4 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first, or date of last contact if neither progression nor death has occurred.

13.5 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

14. DATA AND RECORDS

14.1 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.

14.2 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 Section 7 for information about expedited and routine reporting.
Summary of Data Submission: Refer to the CTSU member website for the table of Required Forms and Materials.

14.3 Global Reporting/Monitoring

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

15. STATISTICAL CONSIDERATIONS

15.1 Study Design

The overall objectives of this study are to assess the activity and toxicity of BAY 80-6946 in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA hotspot mutations. This is a single arm, two-stage, phase II study and no randomization is involved however mutation screening is required. With appropriate consent and authorization, patients will be registered to the screening component of this study. For those who meet all eligibility criteria and have also given an informed consent for the treatment, patient registration to the treatment component will be accomplished in the usual fashion; facilitated by Oncology Patient Enrollment Network (OPEN). There are no treatment comparisons involved. If sufficient activity is noted, the experimental agent may be considered for a future randomized study since a single-arm study will not be able to distinguish between treatment effect and the prognostic effects of the PI3K mutations. With a screen pass rate of 30% and two stages of accrual, 84 patients are expected to be screened and 28 will be enrolled.

15.2 Study Endpoints

To assess the primary objective, the frequency of objective response (complete or partial best overall confirmed response) defined by RECIST 1.1 criteria will be estimated in patients with persistent or recurrent endometrial carcinoma treated with BAY 80-6946. Confirmation of complete and partial responses in tumor evaluations at least 4 weeks apart is required. All registered and eligible patients who received the agent under study will be included in the analysis of the primary objective.

Estimates of the distributions of progression-free survival (PFS) and overall survival (OS) will be estimated using Kaplan-Meier product-limit methods among all eligible patients who received the drug under study.

The safety profile of BAY 80-6946 in recurrent endometrial cancer patients will be assessed using the maximum grade of reported adverse events by term and SOC defined by CTCAE version 4.0. All patients will be evaluable for toxicity from the time of their first treatment with BAY 80-6946 until disease progression or non-protocol therapy is initiated**.**

15.3 Primary Objectives Study Design

15.3.1 Primary Hypothesis and Endpoints

The null hypothesis can be stated as the proportion responding, p, is no more than 5% versus the alternative that the proportion responding is greater than 5%.

15.3.2 How Primary Endpoints Will Be Analyzed

Our general philosophy regarding Phase II trials of new drugs is to facilitate the prompt discovery of inactive agents, yet allow for a reasonable estimate of the response rates for those regimens demonstrating some degree of activity. However, excessive accrual to inactive study regimens to document precise response rates is to be avoided. The purpose of this study is to evaluate the activity and potential toxicity of BAY 80-6946 in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA mutations previously treated with chemotherapy. Our accrual goal is complicated by the administrative logistics of managing the complexity of multi-center trial. Strict adherence to an exact two-stage sampling design with appropriate early stopping rules cannot be practically accomplished due to fluctuating rates of accrual, follow-up requirements, institutional IRB complexities, and the possibility of cases being declared ineligible following central reviews. Nevertheless, monthly decisions regarding the continuance or cessation of accrual will be guided by the following design:

A flexible, minimax 2-stage design chosen for this study to test the null hypothesis that $p \leq 5\%$ with power and sample size calculated under the alternative that $p \geq 25\%$ has an average expected sample size of 18.5 and a probability of early termination of 55%.[21] These average probabilities are computed from the individual probabilities averaged over all permitted accrual combinations and assuming each combination is equally likely. Between 10 and 17 patients (target of 15) will be enrolled onto the treatment component in the first stage of accrual. If the number responding is less than or equal to 0/(10-16) or 1/17, then the study would terminate early and the regimen declared uninteresting. Otherwise, with medical judgment indicating, the study will accrue to a second stage with a cumulative sample size between 21 and 28 (target of 25). If the number of patients responding is less than or equal to 2/(21-22) or 3/(23-28), then the regimen will be declared uninteresting to warrant further investigation. All enrolled patients with recurrent endometrial tumors that are shown to harbor eligible PIK3CA mutations and that initiate study treatment will be included in the analysis of objective response. Exact 95% confidence limits, accounting for the interim analysis, will be provided in the final report.

The patient's best response will be evaluated within the first 6 months on study. Patients alive with a best response of stable disease that is sustained at 6 months but without disease progression will be considered as non-responders for the purpose of the interim and final analyses of the primary endpoint. An additional 6 weeks can be allowed for the purposes of confirming an objective response. Additional data beyond 6 months for these patients can be described in the final study report. **(05/01/2017)**

15.3.3 Sample Size and Power Calculations:

A design was chosen to allow for flexibility in accrual. The target sample size for the first stage is 15 but allowed to vary between 10 and 17. The target sample size for the second stage of accrual is 25 but allowed to vary between 21 and 28. This design, described above, has an average expected sample size of 18.5 and a probability of early termination of 55%. Additionally, the design described above has 90% statistical power under the alternative specified. Type I error is set at 0.05 (one-sided hypothesis test).

15.4 Study Monitoring of Primary Objectives

See section 15.3.2.

15.5 Accrual/Study Duration Considerations

Screening: Genomic analysis was performed on primary endometrial tumors of patients on two legacy GOG studies; 86P[22] and 248.[23] These analyses included identification of any PIK3CA mutations. The studies included patients with advanced or metastatic disease that were either chemotherapy naïve (86P, 248) or had a recurrence following adjuvant chemotherapy (248). For these studies the percentage of sequenced tumors that were identified to have a PIK3CA mutation was 29% (16 of 55) in GOG-0248 and 40% (88 out of 219) in 86P. The distribution of mutation across histologic groups was similar between these two studies. The expected rate of tumors with eligible PIK3CA mutations is expected to be between 20% and 30% among all tumors screened. It is expected that tumors from 4-5 patients will be screened each month.

Possible screening rate for tumors with PIK3CA mutations	Number screened for first stage of accrual (accrual duration)	Total number screened if second stage of accrual is necessary (accrual duration)
20%	75 (18 months)	125 (28 months + interruption*)
30%	50 (12 months)	84 (19 months + interruption*)

*Possible interruption for interim analysis

Treatment trial accrual: Based on past trial experience, the annual accrual is anticipated to be 10-15 patients. The study accrual duration is expected to take 18 months for the first stage and 10 months for the second stage. An interruption in accrual between accrual stages could last as long as 6 months.

Operationally, accrual and initiation of treatment will be monitored and, while there is a target of 15 patients, accrual will automatically be paused by OPEN when the 16th patient is enrolled. This allows for two patients to be enrolled on the same day.

15.6 Dose Level Guidelines

Dose level guidelines are not applicable for this study.

15.7 Secondary or Exploratory Endpoints (including correlative science aims)

15.7.1 Secondary Hypotheses and Endpoints:

The secondary endpoints, progression-free survival, overall survival and adverse events, will be estimated as described in section 15.7.2.

15.7.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Disease progression will be defined using RECIST 1.1 criteria. The duration of progression-free survival and overall survival will be measured from date of study entry onto the treatment component of the study and their distributions will be estimated using Kaplan-Meier product limit estimates. CTCAE version 4.03 will be used to grade and categorize adverse events. Frequencies of maximum grade of adverse events by term or category will be reported. Grade

5 adverse events will be individually reported.

15.7.3 Study Monitoring of Secondary Objectives

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). 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, Developmental Therapeutics Committee and the Safety Review Committee in conjunction with each semi-annual meeting. The initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity.

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 Safety Review Committee. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

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.

15.8 Exploratory Hypothesis and Endpoints

Associations between mutation subtypes and clinical outcomes will be explored using standard statistical methods for categorical and time to event data.

15.9 Gender/Ethnicity/Race Distribution

The accrual distribution by gender, ethnicity and race is provided for the target sample size for two stages. International accrual is not expected.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	0	0	2
White	21	0	1	0	22
More Than One Race	0	0	0	0	0
Total	24	0	1	0	25

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

16. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians. 2015;65:5-29.

2. Bokhman, J. V. Two pathogenetic types of endometrial carcinoma. Gynecol. Oncol. 15, 10–17 (1983).

3. Mutch, D. G. The more things change the more they stay the same. Gynecol. Oncol. 124, 3–4 (2012).

4. Zhao S. Choi M. Overton JD. Bellone S. Roque DM. Cocco E. Guzzo F. et al., Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. Proceedings of the National Academy of Sciences of the United States of America. 110(8):2916-21, 2013

5. Integrated genomic characterization of endometrial carcinoma. The Cancer Genome Atlas Research Network. Nature. 497:67-73, 2013.

6. Vanhaesebroeck, B., Guillermet-Guibert, J., Graupera, M. & Bilanges, B. The emerging mechanisms of isoform-specific PI3K signalling. Nat. Rev. Mol. Cell Biol. 11, 329–341 (2010).

7. Pavlidou, A. & Vlahos, N. F. Molecular alterations of PI3K/Akt/mTOR pathway: a therapeutic target in endometrial cancer. ScientificWorldJournal 2014, 709736 (2014).

8. English, D. P. et al. Oncogenic PIK3CA gene mutations and HER2/neu gene amplifications determine the sensitivity of uterine serous carcinoma cell lines to GDC-0980, a selective inhibitor of Class I PI3 kinase and mTOR kinase (TORC1/2). Am. J. Obstet. Gynecol. 209, 465.e1–9 (2013).

9. English, D. P. et al. HER2/neu gene amplification determines the sensitivity of uterine serous carcinoma cell lines to AZD8055, a novel dual mTORC1/2 inhibitor. Gynecol. Oncol. 131, 753–758 (2013).

10. Chresta, C. M. et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Res. 70, 288–298 (2010).

11. Lopez, S. et al. Taselisib, a selective inhibitor of PIK3CA, is highly effective on PIK3CA-mutated and HER2/neu amplified uterine serous carcinoma in vitro and in vivo. Gynecol. Oncol. (2014). doi:10.1016/j.ygyno.2014.08.024

12. Dancey, J. E. Therapeutic targets: MTOR and related pathways. Cancer Biol. Ther. 5, 1065–1073 (2006).

13. Rodon, J., Dienstmann, R., Serra, V. & Tabernero, J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat. Rev. Clin. Oncol. 10, 143–153 (2013).

14. Janku, F. et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J. Clin. Oncol. 30, 777–782 (2012).

15. Llauradó, M. et al. Molecular bases of endometrial cancer: new roles for new actors in the diagnosis and the therapy of the disease. Mol. Cell. Endocrinol. 358, 244–255 (2012).

16. RuddML, et al., A unique spectrum of somatic PIK3CA (p110α) mutations within primary endometrial carcinomas Clin Cancer Res. 2011 March 15; 17(6): 1331–1340

17. Bellone S., et al., Polymerase ε (POLE) ultra-mutated tumors induce robust tumor-specific CD4+ T cell responses in endometrial cancer patients. Gynecol Oncol. 2015 Jul;138(1):11-7. doi: 10.1016/j.ygyno.2015.04.027. Epub 2015 Apr 27

18. Liu N; Rowley BR; Bull CO; Schneider C; Haegebarth A; Schatz CA; Fracasso PR; Wilkie DP; Hentemann M; Wilhelm SM; Scott WJ; Mumberg D; Ziegelbauer K. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110alpha and p110delta activities in tumor cell lines and xenograft models. Molecular Cancer Therapeutics. 12(11):2319-30, 2013

19. Anonymous. Preliminary results of a phase II study of single agent Bay 80-6946, a Novel PI3K inhibitor, in patients with relapsed/refractory, indolent or aggressive lymphoma. Clinical Advances in Hematology & Oncology. 12(2 Suppl 5):14-6, 2014

20. Pena C.L. et al., Biomarker analysis from a Phase I study of copanlisib with expansion cohorts in solid tumors with and without PIK3CA mutations and NHL. J Clin Oncol 33, 2015 (suppl; abstr 2548)

21. Chen TT, NG T. Optimal flexible designs in phase II clinical trials, Statistics in Medicine. 1998;17:2301-2312.

22. Aghajanian C, Filiaci VL, Dizon DS, Carlson J, Powell MA, Secord AA, Tewari KS, Bender D, O'Malley DM, Stuckey A, Rotmensch J, Levine DA, Lankes HA, Moore KN. A randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer, GOG-86P ASCO 2015 Abstract #144077.

23. Myers AP, Filiaci VL, Zhang Y, Pearl M, Behbakht K, Makker V, Hanjani P, Zweizig S, Burke JJ, Downey G, Leslie KK, Birrer MJ, Fleming GF. Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG Oncology/Gynecologic Oncology Group study ASCO 2015 Abstract #149616

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 – GLYCEMIC INDEX FOR COMMON FOODS

The average Glycemic Index of common foods derived from multiple studies by different laboratories

Foods are categorized as having a low-glycemic index if the glucose reference index is ≤ 55. High-Glycemic Index foods have a glucose reference index >55. The summary table below contains glucose reference for common foods.

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	78 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 5	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roti	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 5	Sweet potato, boiled	63 ± 6
Chapatti	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	53 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	49 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 4						

Dairy products and alternatives		Legumes		Snack products		Sugars	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 4			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

GI = glycemic index.

APPENDIX IV – P-GP, BCRP AND MATE2K SUBSTRATES

P-gp substrates, BCRP substrates and MATE2K-substrates

A list of drugs to be used with caution.

Copanlisib is an inhibitor of BCRP, P-gp and MATE2K *in vitro*. Therefore substrates, especially those with a narrow therapeutic range, should be used with caution.

Pgp-Substrates	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxina[a], everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP substrates	Zidovudine, pantoprazole, cimetidine, sulfasalazine, nitrofurantoin, and several statins (lovastatin, simvastatin, cerivastatin, pitavastatin), mitoxantrone, methotrexate, topotecan, imatinib, and irinotecan
MATE2K-substrates	Metformin, cimetidine, procainamide and N methylnicotinamide

BCRP = Breast cancer resistance protein; MATE2K = Multidrug and toxin extrusion protein 2,
P-gp = Permeability glycoprotein
a:Narrow therapeutic window

APPENDIX V – CYP3A4 INHIBITORS AND INDUCERS

NOTE: As stated in Section 3.3.4, only Strong CYP3A4 inhibitors and inducers should be excluded.

A list of CYP3A4 inhibitors and inducers
This list is not comprehensive. Please refer to a frequently-updated drug information reference for strong CYP3A4 inducers and inhibitors:
http://www.uptodate.com/contents/image?imageKey=CARD/76992&topicKey=HEME%2F1370&source=outline_link&utdPopup=true

Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers
Atazanavir	Amiodarone¶	Carbamazepine	Bexarotene
Boceprevir	Aprepitant	Enzalutamide	Bosentan
Ceritinib	Cimetidine¶	Fosphenytoin	Dabrafenib
Clarithromycin	Conivaptan	Lumacaftor	Dexamethasone¶
Cobicistat and cobicistat containing coformulations	Crizotinib	Mitotane	Efavirenz
Darunavir	Cyclosporine¶	Phenobarbital	Eslicarbazepine
Idelalisib	Diltiazem	Phenytoin	Etravirine
Indinavir	Dronedarone	Primidone	Modafinil
Itraconazole	Erythromycin	Rifabutin	Nafcillin
Ketoconazole	Fluconazole	Rifampin (rifampicin)	St. John's wort
Lopinavir	Fosamprenavir	Rifapentine	
Nefazodone	Fosaprepitant¶		
Nelfinavir	Grapefruit juice		
Ombitasvir-paritaprevir-ritonavir	Imatinib		
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Isavuconazole (isavuconazonium sulfate)		
Posaconazole	Mifepristone		
Ritonavir and ritonavir containing coformulations	Netupitant		
Saquinavir	Nilotinib		
Telaprevir	Tibolone		
Telithromycin	Verapamil		
Voriconazole			

APPENDIX VI: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD (01/09/2017)

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***copanlisib***. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provided need to know:

Copanlisib interacts with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in questions are **CYP3A4 and 1A1.** Copanlisib is broken down by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are **P-gp, BCRP, MATE1, and MATE2K.** Copanlisib is moved in and out of cells/organs by P-gp and BCRP. Copanlisib also inhibits P-gp, BCRP, MATE1, and MATE2K and may affect the clearance of other drugs that are dependent on these transport proteins.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Copanlisib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Copanlisib must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **strong inducers/inhibitors of CYP3A4, 1A1, P-gp, and BCRP or substrates of P-gp, BCRP, MATE1, and MATE2K.**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to

determine if there could be any side effects.

- Avoid smoking as copanlisib may not work as well in people who smoke.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **copanlisib.** This clinical trial is sponsored by the NCI. Copanlisib may interact with drugs that are processed by your liver or use certain transport proteins in your body. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. ➢ Avoid smoking as copanlisib may not work as well in people who smoke.	**Copanlisib** interacts with specific liver enzymes called CYP3A4 and 1A1, transport proteins P-gp, BCRP, MATE1, and MATE2K, and must be used very carefully with other medicines that interact with these enzymes and transporters. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4, 1A1, P-gp, and BCRP."** Copanlisib inhibits **"P-gp, BCRP, MATE1, and MATE2K"** and may affect how other medicines work in your body. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX VII – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (01/09/2017)

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 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

Kits are not provided for this protocol.

III. FFPE Tissue Shipped to the NRG BB-Columbus

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

Primary (FP01) and **metastatic (FM01)** tumor should be collected prior to all treatment.

Only one block may be submitted per tissue type.

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

Mandatory FFPE Biospecimen Requirement

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 15 unstained slides (10 charged, 5µm, and 5 uncharged, 10 µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Completing Form TR for FFPE Biospecimens

The type of specimen (block, slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

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 GY008)
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. 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 PDF of Form TR in a "SEDES style" format. 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 Support if you need assistance (Email: support@nrgoncology.org; Phone: 716-845-7767).

V. Shipping Translational Science Biospecimens
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 GY008
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.

VI. 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.

APPENDIX VIII – BLOOD GLUCOSE DIARY

Patient Name/ID: _____

Please record your blood glucose levels as instructed by your doctor. Return this diary to your doctor at your next visit.

Date	Wake-Up (pre-bkfst)	Pre-Lunch	Afternoon	Pre-Dinner	Bedtime (pre-snack)