MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2020-1241
Protocol Title	Phase 2 study of PI3K inhibitor copanlisib in combination with fulvestrant in selected ER+ and/or PR+ cancers with PI3K (PIK3CA, PIK3R1) and/or PTEN alterations
Protocol Phase	2
Protocol Version	3.0
Version Date	19 October 2022
Protocol PI	[redacted]
[redacted]	[redacted]
ClinicalTrials.gov Identifier	NCT05082025
IND Sponsor	MD Anderson Cancer Center
IND #	[redacted]

[redacted]

This study will be conducted in compliance with U.S. FDA regulations, ICH Guidelines, the principles of the Helsinki Agreement, and all other applicable state or local requirements.

TABLE OF CONTENTS

List of Abbreviations and Definition of Terms

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AST	Aspartate transaminase
AUC24h	Area under the curve at 24 hours
B.I.D	Twice daily
BOR	Best overall response
BP	Blood pressure
BCRP	Breast cancer resistance protein
CBC	Complete blood count
CBHM	Calibrated bayesian hierarchical model
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
C_{max}	Maximum concentration
CNS	Central nervous system
CORe	Clinical Oncology Research e-database
COSMIC	Catalogue of Somatic Mutations in Cancer
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
C_{trough}	Trough concentration
CYP	Cytochrome P450
DLT	Dose-limiting toxicity

Abbreviation or special term	Explanation
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMR	Electronic medical record
ER+	Estrogen receptor-positive
EOT	End-of-treatment
eSAE	Electronic serious adverse event application
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HR+	Hormone receptor-positive
IB	Investigator's brochure
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
IHC	Immunohistochemistry
IM	Intramuscular(ly)
IND	Investigational new drug
IRB	Institutional review board
IV	Intravenous(ly)
Kd	Dissociation constant
MATE	Multidrug and toxin extrusion protein
MDACC	MD Anderson Cancer Center
MOCLIP	Molecular and Clinical Data Integrated Platform
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
mTOR	Mammalian target of rapamycin
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next-generation sequencing
NHL	Non-Hodgkin's lymphoma
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal investigator
PI3K	Phosphatidylinositol-3 kinase
PI3Ki	Phosphatidylinositol-3 kinase inhibitor
PR	Partial response
PR+	Progesterone receptor-positive
PJP	Pneumocystis jiroveci pneumonia
RECIST	Response Evaluation Criteria in Solid Tumors
RNAseq	RNA sequencing
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SERD	Selective estrogen receptor degrader
SOC	Standard of care
TB	Total bilirubin

Abbreviation or special term	Explanation
TCGA	The Cancer Genome Atlas
Treg	Regulatory CD4+ T-cell
ULN	Upper limit of normal
WBC	White blood cell

CLINICAL STUDY SYNOPSIS

Protocol Title:	Phase 2 study of PI3K inhibitor copanlisib in combination with fulvestrant in selected ER+ and/or PR+ cancers with PI3K (PIK3CA, PIK3R1) and/or PTEN alterations
IND Number:	157719
Protocol Number:	21897/ 2020-1241
Principal Investigator:	[redacted]
Study Phase:	Phase 2
Investigational Products:	Copanlisib and fulvestrant
Study Indications:	Solid tumors: ovarian cancer, endometrial cancer, breast cancer
Study Centers:	MD Anderson Cancer Center (single-center study)
[redacted]	
Length of study:	2 years
Objectives:	The objective of this phase 2 basket study is to evaluate the efficacy and safety of copanlisib in combination with fulvestrant administered to subjects with selected estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+) advanced or metastatic solid tumors with PI3K and/or PTEN alterations. The study will have two parts. **Part 1: Dose confirmation:** [redacted]

	Secondary Objectives: • To assess the efficacy of copanlisib administered in combination with fulvestrant as outlined in Part 2 by evaluating the objective response rate (ORR). • To evaluate additional efficacy measures such as progression-free survival (PFS) and overall survival (OS) of copanlisib in combination with fulvestrant. **Exploratory Objective:** • To investigate clonal evolution, and mechanisms of resistance using tissue and liquid biopsies utilizing circulating tumor DNA (ctDNA) as outlined in Part 2. **Part 2: Dose expansion:** **Primary Objectives:** • To assess the efficacy of copanlisib administered in combination with fulvestrant as outlined above by evaluating the objective response rate (ORR). Patients enrolled for Part 1 will be included in this efficacy analysis. **Secondary Objectives:** • To evaluate additional efficacy measures such as PFS and OS of copanlisib in combination with fulvestrant. • To evaluate the safety and tolerability of copanlisib in combination with fulvestrant. **Exploratory Objective:** • To investigate clonal evolution, and mechanisms of resistance using tissue and liquid biopsies utilizing ctDNA.
Purpose/ Rationale:	The purpose of this study is to evaluate the efficacy and safety of copanlisib in combination with fulvestrant in advanced hormone receptor-positive (HR+) solid tumors harboring alterations that activate the Phosphatidylinositol-3 kinase (PI3K) pathway. Copanlisib is a potent pan-PI3K inhibitor (PI3Ki) approved by the Food and Drug Administration (FDA) for the treatment of patients with relapsed follicular lymphoma. Fulvestrant is a selective ER degrader (SERD) and is FDA-approved to treat HR+ metastatic breast cancer. The Phase 3 SOLAR-1 trial demonstrated the efficacy of the PI3K-α specific inhibitor alpelisib in combination with fulvestrant in the treatment of *PIK3CA*-mutated, hormone receptor HR+ advanced or metastatic breast cancer refractory to hormone regimen (1). Given the findings of the SOLAR-1 trial, we hypothesize that the clinical benefit of the PI3K pathway inhibitors and endocrine therapy combination can be extended to other HR+ solid cancers harboring alterations that activate the PI3K pathway. Estrogen and/or progesterone receptors are commonly expressed in the ovarian, endometrial, salivary

	gland, and other cancers (2). Furthermore, we and others found that *PIK3CA* mutations frequently co-occur in these HR-expressing cancers (3-8). Endocrine therapies, including fulvestrant, have been investigated for use in the treatment of gynecological malignancies and have demonstrated modest single-agent clinical activity (9-11). Similar to breast cancer, efficacy is limited by *de novo* and acquired endocrine resistance, and endocrine resistance can be overcome by PI3K pathway inhibition (12-14). In addition, our group and others have demonstrated that combinations of mammalian target of rapamycin (mTOR) inhibitors with hormone therapy can be effective in gynecological malignancies (14, 15).
Study Design:	We propose to conduct a multi-arm, open-label, phase 2 basket trial investigating the efficacy and safety of copanlisib in combination with fulvestrant in patients with selected HR+ advanced or metastatic solid cancers, harboring PI3K or *PTEN* alterations including ovarian cancer (cohort 1), endometrial cancer (cohort 2), and breast cancer (cohort 3). [redacted]
Study Population:	The study population will consist of subjects with selected HR+ (ER+ or/and PR+) advanced or metastatic solid tumors with PI3K (*PIK3CA, PIK3R1*) and/or *PTEN* alterations with ovarian, endometrial and breast cancer. Patients must have no available standard

	therapy known to prolong survival or are not candidates for such a therapy. The study [redacted]
Key Inclusion Criteria	1. Histologically confirmed ER+ and/or PR+ advanced or metastatic solid cancer including ovarian cancer (cohort 1), endometrial cancer (cohort 2), or breast cancer (cohort 3) **(Figure 1).** ER and/or PR positivity is defined as >10% immunohistochemical staining of any intensity. Cohort 3 will be enriched to include at least 7 patients naïve to any PI3Ki in Stage 1 and also in Stage 2. 2. Presence of one or more PI3K and/or PTEN alterations in tumor tissue. Genetic alterations will include *PIK3CA* gain of function mutations, *PIK3R1* loss of function mutations, *PTEN* loss of function mutations, and *PTEN* deletions. 3. Measurable disease per the RECIST 1.1. 4. The patient (or legally acceptable representative, if applicable) provides written informed consent for the study. 5. Female or male ≥18 years of age on the day of informed consent signing. 6. Patients have no available standard therapy known to prolong survival. For cohort 3 only, prior treatment with aPI3Ki or everolimus is not required and patients with or without prior PI3Ki or everolimus will be qualified for enrollment 7. Adequate archived tumor tissue for the analysis for PI3K and PTEN alterations if available. 8. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. 9. Adequate organ and marrow function as defined below: a. Hemoglobin ≥9.0 g/dL b. Absolute neutrophil count ≥1.5 × 10^9/L c. Platelet count ≥100 × 10^9/L

	d. Total bilirubin (TB) ≤1.5 × institutional upper limit of normal (ULN); Patients with known Gilbert's disease who have TB ≤3 × ULN may be enrolled) e. Aspartate transaminase (AST)/ alanine transaminase (ALT) ≤3 × ULN. If patient has liver metastases, AST and ALT ≤5.0 × ULN. f. Creatinine ≤1.5 x ULN g. International normalized ratio ≤1.5. 10. Fasting blood glucose ≤140 mg/dL and hemoglobin A1c ≤8.5% (both criteria have to be met). 11. Cardiac ejection fraction ≥45%. 12. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 14 days prior to the initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Women of childbearing potential (WOCBP) must agree and commit to the use of 2 highly effective methods of birth control throughout the duration of the study until at least 150 days following the last dose of study drug. Acceptable methods are defined as those that result, alone or in combination, in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. Women using systemically acting hormonal contraceptives should add a barrier method. In certain countries (if permitted by law), WOCBP may agree to abide by heterosexual sexual abstinence during the time of participation in this study. 13. Male patients and their female partners of childbearing potential must agree and commit to use a barrier contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until at least 90 days following the last dose of study drug, in addition to their female partners using either an intrauterine device or hormonal contraception and continuing until at least 90 days following the last dose of study drug. This criterion may be waived for male patients who have had a vasectomy > 6 months before signing the ICF. 14. Willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
Key Exclusion Criteria	1. The patient has central nervous system (CNS) involvement. If the patient fulfills the following 3 criteria, she/he is eligible for the study: a. Completed prior therapy (including radiation and/or surgery) for CNS metastases, and b. CNS tumor is radiologically stable for ≥28 days prior to study start, and c. The patient is not receiving steroids and enzyme-inducing antiepileptic medications for brain metastases. 2. Patients with HER2 positive breast cancer.

3. Patients must be ≥4 weeks or at least 5 half-lives beyond treatment with any chemotherapy or other investigational therapy including hormonal, biological, or targeted agents at the time of treatment initiation.
   - NOTE: If the patient received major surgery, she/he must have recovered adequately from the toxicity and/or complications from the intervention prior to starting the study treatment.
4. Prior treatment with fulvestrant or any PI3Ki for cohorts 1 and 2.
5. Known hypersensitivity to copanlisib or fulvestrant, or to any of the excipients of copanlisib or fulvestrant.
6. Concomitant use of strong cytochrome P450 (CYP)3A4 inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) or inhibitors (e.g., ritonavir, saquinavir, nelfinavir, boceprevir, telaprevir, ketoconazole, omeprazole). Use of strong inhibitors and/or inducers of CYP3A4 is not permitted from Day -14 of Cycle 1 until the start of the study intervention.
7. The patient is currently receiving warfarin or other coumarin derived anticoagulants for treatment, prophylaxis, or otherwise. Therapy with heparin, low molecular weight heparin, fondaparinux, or direct oral anticoagulants such as rivaroxaban or apixaban is allowed.
8. Known additional malignancy that is progressing or requires active treatment.
9. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
10. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
11. Known history of human immunodeficiency virus infection.
12. History or current symptomatic pneumonitis.
13. Has clinically significant, uncontrolled heart disease and/or recent cardiac events, including any of the following:
    a. History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
    b. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    c. Documented cardiomyopathy
    d. History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months
    e. Uncontrolled hypertension defined by a systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg, with or without antihypertensive medication over the course of one clinic visit at intervals of ≥30 minutes. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
14. Type 1 diabetes mellitus.
15. Uncontrolled type 2 diabetes mellitus.

	16. Positive cytomegalovirus (CMV) polymerase chain reaction (PCR) test at baseline. 17. Active hepatitis B virus (HBV; chronic or acute; defined as having a known positive hepatitis B surface antigen [HbsAg] test at the time of screening) or hepatitis C infection requiring treatment. • Participants with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HbcAb] and absence of HbsAg) are eligible if HBV DNA is negative. • Participants with positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.
[redacted]	
Study endpoints:	**Efficacy endpoints:** Radiographic tumor assessments (computed tomography [CT] scan or magnetic resonance imaging [MRI]) will be performed by RECIST 1.1. The endpoints of efficacy assessment include: • ORR described as the proportion of patients who achieve CR or PR by the combination therapy. • PFS described as the time from study treatment initiation to the date of disease progression or death due to any cause. Patients without progression will be censored at the time of the last follow up. • OS described as the time from study treatment initiation to the date of death due to any cause. Patients without progression will be censored at the time of the last follow up. **Safety endpoints:** • Incidence of AEs including but not limited to treatment-emergent AEs, serious AEs, deaths, and clinical laboratory abnormalities, as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. • DLT is defined as any of the following adverse reaction observed during first cycle of treatment, and assessed as *possibly*, *probably* or *definitely* related to treatment with copanlisib in combination with fulvestrant. NCI CTCAE v. 5.0 will be used for grading of AEs. ○ **Non-hematological AEs:**

- Grade ≥2 non-infectious pneumonitis
- Laboratory abnormalities meeting Hy's law criteria (AST or ALT >3 × ULN with concomitant TB >2 × ULN). (FDA 2009)
- Any ≥Grade 3 AE, except:
  - Grade 3 fatigue lasting ≤5 days
  - Grade 3 nausea or vomiting that has resolved to grade ≤ 2 within 3 days after standard antiemetic therapies
  - Grade 3 diarrhea that has resolved to grade ≤2 within 3 days after standard antidiarrheal therapies
  - Isolated laboratory findings not associated with signs or symptoms and lasting less than 3 days, including but not limited to grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and grade 3 electrolyte laboratory abnormalities hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to supplementation and grade 3/4 lymphopenia.
  - Grade 3 hyperglycemia lasting ≤7 days

- **Hematological AEs:**
  - Grade 4 neutropenia lasting ≥7 consecutive days
  - Grade 3 and grade 4 febrile neutropenia
  - Grade 4 anemia (in the absence of disease progression in bone marrow)
  - Grade 3 anemia requiring blood transfusion
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia lasting ≥7 consecutive days or associated with bleeding

- **The following event is classified as a DLT:**
  - If a full cycle of copanlisib (3 doses) will not be completed due to any study intervention-related AE, the AE is considered as a DLT
  - A delay of over 1 week in initiating Cycle 2 of copanlisib and/or fulvestrant treatment occurs secondary to any study drug related AE, the AE will be considered a DLT

- Death not clearly attributed to underlying disease or alternative cause

Note: Allergic reactions leading to discontinuation of study interventions will not be considered as a DLT and participant will be replaced.

Exploratory endpoints:
Biomarker-based studies will be conducted using tumor tissue and liquid biopsies to assess clonal evolution, and mechanisms of innate and adaptive resistance.

Tumor biopsies, if medically feasible, will be obtained at screening (within 28 days of Cycle 1, Day 1), on-treatment after fulvestrant and copanlisib administration on Cycle 2 Day 1, and at End-of-treatment (EOT). Tumor biopsies will be optional but encouraged, especially in patients with a response or prolonged disease control **(Figure 2 and Appendix A: Schedule of Assessments).** Examples of studies include identification of genomic biomarkers of response and intrinsic or adaptive resistance by whole exome, targeted next-generation sequencing (NGS), Nanostring DSP, or other similar methods.

Mandatory blood samples to isolate plasma ctDNA will be collected at pre-treatment (Day -28 to Day 1 of Cycle 1), on-treatment (pre-dose -at the same time as the on treatment biopsy- on Cycle 2 Day 1 as well as at the first two restaging visits), and post-treatment at EoT. **(Figure 2 and Appendix A: Schedule of Assessments)**.

Plasma ctDNA samples will be used to evaluate changes in ctDNA quantity and clonal evolution by selected molecular methods that may include targeted NGS, methylation sequencing, and droplet digital polymerase chain reaction..

[redacted]

[redacted]

Duration of the study	Patients will receive the combination treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study treatment for any other reason.

	Patients will be eligible to receive study treatment for as long as the investigator, the sponsor, and the supporting company agree that the patient is showing clinical benefit.

1 BACKGROUND AND RATIONALE

Hormone receptor (HR) expression is a common feature of gynecological cancers similar to breast cancer. Among the most common gynecological cancers, 60%- 87% of endometrial and 20%-98% of ovarian cancers are ER+ and/or PR+ depending on the specific subtype (2, 17-23). The recommended treatment for patients with HR+ cancers includes endocrine therapy, alone or combination with chemotherapy or targeted therapy (24-26). However, resistance develops, and disease progression eventually happens (27).

The PI3K/AKT/mTOR signaling pathway is one of the most frequently dysregulated pathways in human cancer (28-33). PI3K/AKT/mTOR pathway regulates critical cellular activities such as proliferation, metabolism, and motility that promote the growth and survival of cancer cells (34). The PI3K/AKT/mTOR pathway can be aberrantly activated by multiple factors, including diverse oncogenic genomic alterations in *PIK3CA, PIK3R1, PTEN, AKT, TSC1, TSC2, LKB1, mTOR*, and other critical genes (5, 35-44). PTEN negatively regulates PI3K pathway by converting phosphatidyl-inositol-3,4,5-trisphosphate (PIP3) to phosphatidyl-inositol-4-5-bisphosphate (PIP2) (45, 46). PI3Kβ isoform is the driver of PTEN-null cancers (47). Pan-Class I PI3K or PI3Kβ-specific inhibitors can be used to target PTEN-deficient tumors. Loss of PTEN and increased PI3K signaling have been implicated in resistance to endocrine therapies in ER+ breast cancer, indicating that alterations in PI3K/AKT/mTOR pathway might also contribute to resistance in other HR+ gynecological cancers to endocrine therapies (3, 48-51).

Endometrial cancer is the leading gynecological cancer in the United States and is characterized by an activated PI3K pathway as a result of *PTEN* inactivating and/or *PIK3CA-activating* and *PIK3R1-in*activating alterations (52). 63%, 39%, and 33% of endometrial cancers harbor inactivating *PTEN* alterations according to The Cancer Genome Atlas (TCGA) studies, Catalogue of Somatic Mutations in Cancer (COSMIC) database, and a study from our group, respectively. *PIK3CA* and *PIK3R1* mutations were identified in 25-52% and 22-28% of endometrial cancers, respectively (28, 53, 54). Interestingly, *PIK3CA* and *PTEN* are frequently mutated simultaneously in endometrial cancers (28, 52).

Ovarian cancer is the most lethal gynecological malignancy in the United States and other developed countries. According to the TCGA study, *PIK3CA* is altered in 21% of ovarian cancers. More than 90% of the *PIK3CA* alterations in ovarian cancers are gene amplifications. Alterations in *PTEN* and *PIK3R1* are also identified in ovarian cancers at lower rates (6% and 3%, respectively) (54).

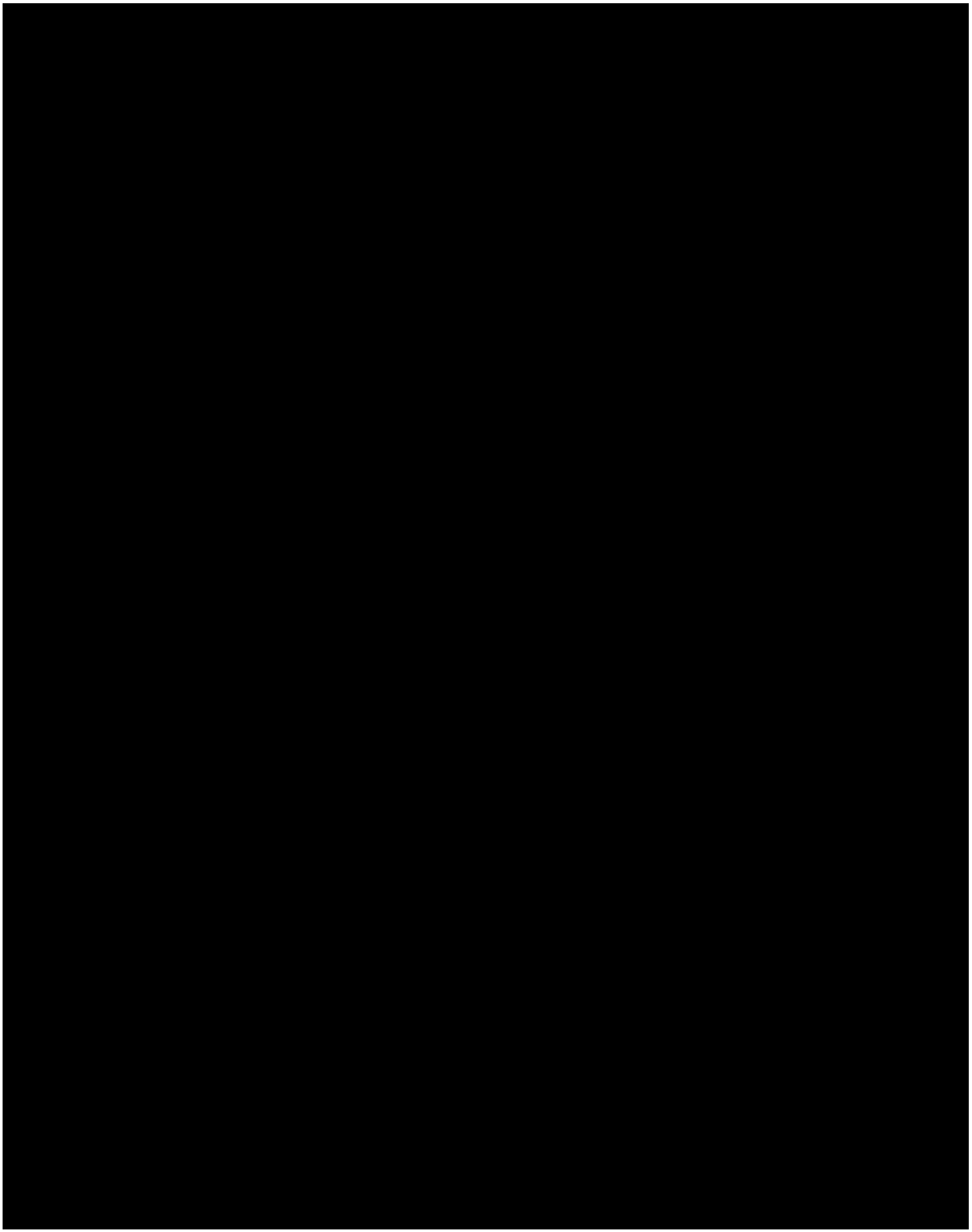
Investigations of the therapeutic targeting of the PI3K/AKT/mTOR pathway have resulted in the development of several distinct classes of pathway inhibitors, including PI3K and AKT inhibitors, as well as allosteric mTOR and catalytic mTOR kinase inhibitors (28). Despite the significant effort invested in the preclinical and clinical development of compounds targeting the PI3K/AKT/mTOR pathway, only a few have been approved for clinical use. There are several possible reasons for this lack of headway (55-59). Most inhibitors of the oncogenically activated PI3K/AKT/mTOR pathway have low ORRs when used as monotherapy (55, 56). The relatively modest activity is

often explained by negative feedback loops that result in pathway reactivation (6, 60-63). Early clinical data suggest that combinations of inhibitors targeting the PI3K/AKT/mTOR pathway are more effective than inhibitor monotherapies (5, 7).

[redacted]

Supporting the concept, pan-PI3Ki buparlisib in combination with fulvestrant doubled the median PFS in patients with *PIK3CA*-mutant versus wild-type advanced breast cancer as demonstrated in 2 phase 3 trials (64, 65). Another Phase 1 trial tested the mTOR inhibitor everolimus in combination with aromatase inhibitor anastrozole in advanced gynecological and breast malignancies. Everolimus- anastrozole combination achieved SD/PR/CR in 24% of patients (n=50) (15) The clinical benefit of the PI3K pathway inhibitors and endocrine therapy combination can be extended to other HR+ solid cancers harboring alterations that activate the PI3K pathway.

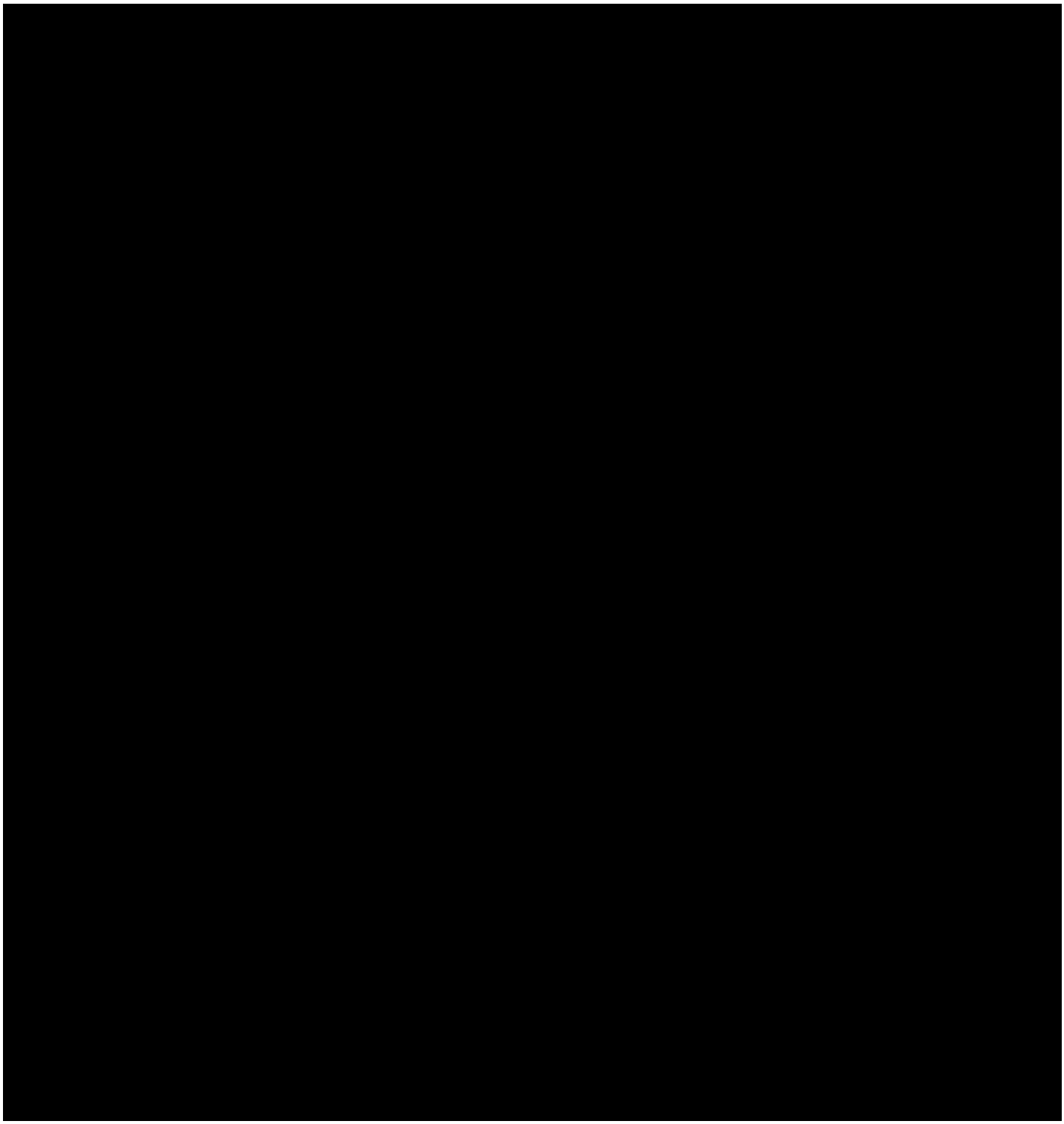
[redacted]



Class I PI3K subfamily is comprised of four isoforms; PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ. All of these isoforms have a catalytic P110 subunit (66, 67). PI3Kα signaling is frequently implicated in a variety of cancer types. Tumors harboring alterations activating *PIK3CA* or de-activating *PTEN* are sensitive to PI3Kα inhibitors. Specific inhibition of PI3Kδ demonstrated remarkable therapeutic efficacy in certain human leukemias and lymphomas (68). PI3Kδ inhibition in B-cell malignancies prevents tumor cells from responding to supportive stimuli from the microenvironment (69). Mice experiments have shown that PI3Kδ inhibition can protect against a variety of cancers, including solid tumors, by breaking the regulatory CD4+ T-cell (Treg)-mediated immune tolerance to activate cytotoxic T- cell response (70).

Copanlisib is approved for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies (FDA, 2017).

[redacted]



1.2 Fulvestrant

Fulvestrant (Faslodex®) is a competitive ER antagonist that causes degradation of ER upon binding. Fulvestrant significantly down-regulates ER protein and also PR expression consistent with a lack of intrinsic estrogen agonist effects. It is approved for use in the following indications:

- HR+, human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
- HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- HR+, HER2- advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine-based therapy or following disease progression on endocrine therapy.
- HR+, HER2- advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

For more information, refer to the prescribing information.

1.2.1 Safety

The most common, clinically significant adverse reactions occurring in ≥5% of patients receiving Fulvestrant 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation.

Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of Fulvestrant patients and were not dose-dependent.

There may be overlapping toxicity when combining copanlisib with fulvestrant, based on current clinical experience: gastrointestinal disorders (e.g., nausea), asthenia, and rash have been observed with both copanlisib and fulvestrant.

Increased exposure to fulvestrant is observed in the case of hepatic impairment. Therefore, caution is required when administering the combination of fulvestrant and copanlisib to patients with impaired liver function.

1.3 RATIONALE

1.3.1 Study Rationale and Purpose

The purpose of this study is to evaluate the efficacy and safety of copanlisib in combination with fulvestrant in advanced HR+ solid tumors harboring alterations that activate the PI3K pathway. Copanlisib is a potent pan-PI3Ki approved by the FDA for the treatment of patients with relapsed follicular lymphoma. Fulvestrant is a SERD and is FDA-approved to treat HR+ metastatic breast cancer in addition to other cancers.

Estrogen and/or progesterone receptors are commonly expressed in the ovarian, endometrial, salivary gland, and other cancers (2). Furthermore, we and others found that *PIK3CA-activating, PTEN-inactivating and PIK3R1-inactivating* mutations frequently occur in these HR-expressing cancers (3-8, 54). Functional inactivation of PTEN by mutations, loss of copy number and epigenetic silencing leads to aberrant activation of PI3K/AKT/mTOR pathway, increasing growth, invasion and metastasis of a diverse set of tumors including breast, endometrial, prostate, renal cell, hepatocellular, glioblastoma and colorectal cancers (75-77).

Endometrial cancer is the leading gynecological cancer in the United States and is characterized by an activated PI3K pathway as a result of *PTEN*-inactivating and/or *PIK3CA-activating* and *PIK3R1*-inactivating alterations (52). 63%, 39%, and 33% of endometrial cancers harbor inactivating *PTEN* alterations according to The Cancer Genome Atlas (TCGA) studies, Catalogue of Somatic Mutations in Cancer (COSMIC) database, and a study from our group, respectively. *PIK3CA* and *PIK3R1* mutations were identified in 25-52% and 22-28% of endometrial cancers, respectively (28, 53, 54). Interestingly, *PIK3CA* and *PTEN* are frequently mutated simultaneously in endometrial cancers (28, 52). Ovarian cancer is the most lethal gynecological malignancy in the United States and other developed countries. According to the TCGA study, *PIK3CA* is altered in 21% of ovarian cancers. More than 90% of the *PIK3CA* alterations in ovarian cancers are gene amplifications. Alterations in *PTEN* and *PIK3R1* are also identified in ovarian cancers at lower rates (6% and 3%, respectively) (54).

Activation of PI3K/AKT/mTOR pathway has also been implicated in resistance to endocrine therapies in ER+ breast cancer, indicating that alterations in PI3K/AKT/mTOR pathway might also contribute to resistance in other HR+ gynecological cancers to endocrine therapies (3, 48, 49). Endocrine therapies, including fulvestrant, have been investigated for use in the treatment of gynecological malignancies and have demonstrated modest single-agent clinical activity (9-11). Similar to breast cancer, efficacy is limited by *de novo* and acquired endocrine resistance, and endocrine resistance can be overcome by PI3K pathway inhibition (12-14). Also, our group and others have demonstrated that combinations of mTOR inhibitors with hormone therapy can be effective in gynecological malignancies (14, 15).

PI3K blockade, in combination with hormone therapy, demonstrated clinical activity in different gynecological and breast cancers. Specifically, the Phase 3 SOLAR-1 trial demonstrated the efficacy of the PI3K-α specific inhibitor alpelisib in combination with fulvestrant in the treatment of *PIK3CA*-mutated, hormone receptor HR+ advanced or metastatic breast cancer refractory to hormone regimen (1). Given the findings of the SOLAR-1 trial, we hypothesize that the clinical benefit of the PI3K pathway inhibitors and endocrine therapy combination can be extended to other HR+ solid cancers harboring alterations that activate the PI3K pathway.

2 STUDY OBJECTIVES

The objective of this phase 2 basket study is to evaluate the efficacy and safety of copanlisib in combination with fulvestrant administered to subjects with selected ER+ and/or PR+ advanced or metastatic solid tumors with PI3K and/or PTEN alterations

2.1 Part 1: Dose confirmation:

Primary Objective:

- To evaluate the safety, tolerability, and DLTs of copanlisib 60 mg administered IV on Days 1, 8 and 15 in combination with fulvestrant 500 mg administered IM on Day 1 and Day 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle to confirm the RP2D of the combination therapy.

Secondary objectives:

- To assess the efficacy of copanlisib administered in combination with fulvestrant as outlined in Part 2 by evaluating the ORR.
- To evaluate additional efficacy measures such as PFS and OS of copanlisib in combination with fulvestrant.

Exploratory Objective:

- To investigate clonal evolution, and mechanisms of resistance using tissue and liquid biopsies utilizing ctDNA as outlined in Part 2.

2.2 Part 2: Dose expansion:

Primary objective:

- To assess the efficacy of copanlisib administered in combination with fulvestrant as outlined above by evaluating the ORR. Patients enrolled for Part 1 will be included in this efficacy analysis.

Secondary Objectives:

- To evaluate additional efficacy measures such as PFS and OS of copanlisib in combination with fulvestrant.
- To evaluate the safety and tolerability of copanlisib in combination with fulvestrant.

Exploratory Objective:

- To investigate clonal evolution, and mechanisms of resistance using tissue and liquid biopsies utilizing ctDNA.

3 STUDY ENDPOINTS

3.1 Efficacy endpoints:

Radiographic tumor assessments (CT scan or MRI) will be performed by RECIST 1.1. The endpoints of efficacy assessment include:

- ORR described as the proportion of patients who achieve CR or PR by the combination therapy.
- PFS described as the time from study treatment initiation to the date of disease progression or death due to any cause. Patients without progression will be censored at the time of the last follow up.
- OS described as the time from study treatment initiation to the date of death due to any cause. Patients without progression will be censored at the time of the last follow up.

3.2 Safety endpoints:

- Incidence of AEs including but not limited to treatment-emergent AEs, serious AEs, deaths, and clinical laboratory abnormalities, as assessed by the NCI CTCAE v5.0.
- DLT is defined as any of the following adverse reaction observed during first cycle of treatment, and assessed as *possibly*, *probably* or *definitely* related to treatment with copanlisib in combination with fulvestrant. NCI CTCAE v. 5.0 will be used for grading of AEs.
    - **Non-hematological AEs:**
        - Grade ≥2 non-infectious pneumonitis
        - Laboratory abnormalities meeting Hy's law criteria (AST or ALT >3 × ULN with concomitant TB >2 × ULN). (FDA 2009)
        - Any ≥Grade 3 AE, except:
            - Grade 3 fatigue lasting ≤5 days
            - Grade 3 nausea or vomiting that has resolved to grade ≤2 within 3 days after standard antiemetic therapies
            - Grade 3 diarrhea that has resolved to grade ≤2 within 3 days after standard antidiarrheal therapies
            - Isolated laboratory findings not associated with signs or symptoms and lasting less than 3 days, including but not limited to grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and grade 3 electrolyte laboratory abnormalities hypophosphatemia, hypokalemia,

hypocalcemia, or hypomagnesemia responsive to supplementation and grade 3/4 lymphopenia.

- Grade 3 hyperglycemia lasting ≤7 days

- **Hematological AEs:**
  - Grade 4 neutropenia lasting ≥7 consecutive days
  - Grade 3 and grade 4 febrile neutropenia
  - Grade 4 anemia (in the absence of disease progression in bone marrow)
  - Grade 3 anemia requiring blood transfusion
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia lasting ≥7 consecutive days or associated with bleeding

- **The following event is classified as a DLT:**
  - If a full cycle of copanlisib (3 doses) will not be completed due to any study intervention-related AE, the AE is considered as a DLT
  - A delay of over 1 week in initiating Cycle 2 of copanlisib and/or fulvestrant treatment occurs secondary to any study drug related AE, the AE will be considered a DLT
  - Death not clearly attributed to underlying disease or alternative cause

Note: Allergic reactions leading to discontinuation of study interventions will not be considered as a DLT and participant will be replaced.

3.3 Exploratory endpoints:

Biomarker-based studies will be performed using tumor tissue and liquid biopsies to assess clonal evolution, and mechanisms of innate and adaptive resistance.

Tumor biopsies, if medically feasible, will be obtained at screening (within 28 days of Cycle 1, Day 1) on-treatment after fulvestrant and copanlisib administration on Cycle 2 Day 1 and at EOT. Biopsies will be optional but encouraged, especially in patients with a response or prolonged disease control**.** Examples of studies include identification of genomic biomarkers of response and intrinsic or adaptive resistance by whole exome, targeted NGS, and Nanostring DSP or other similar methods.

Mandatory blood samples to isolate plasma ctDNA will be collected at pre-treatment (Day -28 to Day1 of Cycle 1), on-treatment (pre-dose -at the same time as the on treatment biopsy- on Cycle 2 Day 1 as well as at the first two restaging visits), and post-treatment at EoT.
Plasma ctDNA samples will be used to evaluate changes in ctDNA quantity and clonal evolution by selected molecular methods that may include targeted NGS, methylation sequencing, and droplet digital polymerase chain reaction.

4 INVESTIGATIONAL PLAN

4.1 Study Design

We propose to conduct a multi-arm, open-label, phase 2 basket trial investigating the efficacy and safety of copanlisib in combination with fulvestrant in patients with selected HR+ advanced or metastatic solid cancers, harboring PI3K or PTEN alterations including ovarian cancer (cohort 1), endometrial cancer (cohort 2), and breast cancer (cohort 3). Cohort 3 will be enriched to include at least 7 patients naïve to any PI3Ki in Stage 1 and also in Stage 2.

and will be contacted by telephone every 12 weeks (±14 days) for survival status until death, withdrawal of consent, or lost to follow-up.

Exploratory biomarker studies using pre-treatment, on-treatment, and post-progression tumor biopsy tissues and serially collected blood liquid biopsies will investigate clonal evolution, and mechanisms of innate and adaptive resistance.

The study will consist of a screening/baseline phase, treatment phase, safety follow-up, follow-up visits, and survival follow-up.

4.1.1 Screening/Baseline Phase

Written informed consent is required before performing any study-specific tests or procedures. The signing of the informed consent form (ICF) can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before study entry. Results of the standard of care (SOC) tests or examinations performed before obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests. The investigator or designee will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

The use of remote consenting to obtain informed consent from clinical trial participants using paper or electronic consent forms is allowed in this study.

Evaluations for PI3K and/or PTEN alterations and hormone receptor status will be performed by a U.S. Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathologists-accredited clinical laboratory.

Baseline assessments will be performed within 28 days of study treatment initiation unless specified otherwise.

4.1.2 Treatment Phase

[redacted]

treatment in the opinion of the investigator, the patient is clinically asymptomatic, and continuation of study treatment is approved by the sponsor.
Assessments will be performed at the time points specified in the Schedule of Assessments (Appendix A).

4.1.3 Safety Follow-Up

The safety follow-up visit should be conducted 30 (+ 5) days after the last dose of study treatment or before the initiation of a new anticancer therapy, whichever comes first. AEs that occur prior to the safety follow-up visit will be recorded as per the NCI Adverse Events Recording Guidelines for Phase II trials. Patients with an AE of > Grade 1 will be followed until the resolution of the AE to ≤Grade 1 or baseline. Serious AEs (SAEs) that occur within 30 days of EOT should also be followed and recorded.

4.1.4 Follow-Up Visits

Patients who discontinue study treatment for a reason other than disease progression will move into the follow-up phase. Patients will be monitored for disease status by tumor imaging (CT scan or MRI, as appropriate) every 8 weeks (±7 days) until PD, death, initiation of new anticancer therapy, withdrawal of consent, or lost to follow-up.

4.1.5 Survival Follow-Up

Patients who experience confirmed disease progression or initiate a new anticancer therapy will move into the survival follow-up phase. Patients will be contacted by telephone every 12 weeks (±14 days) for survival status until death, withdrawal of consent, or lost to follow-up.

4.1.6 Pharmacodynamic Assessments

In patients with accessible tumor, tumor biopsies may be obtained at Screening (within 28 days of Cycle 1 Day 1) on-treatment after fulvestrant and copanlisib administration on Cycle 2 Day 1, and at EOT. Tumor biopsies will be optional but encouraged, especially in patients with a response or prolonged disease control. Tumor biopsies will be used to evaluate genomic biomarkers of response and intrinsic and adaptive resistance.

Mandatory blood samples to isolate plasma ctDNA will be collected at pre-treatment (Day -28 to Day 1 of Cycle 1), on-treatment (pre-dose -at the same time as the on treatment biopsy- on Cycle 2 Day 1 as well as at the first two restaging visits), and post-treatment at EOT. Tissue and plasma ctDNA will be used to evaluate molecular and genetic biomarkers of response and resistance to study treatment. ctDNA analyses may include genomic profiling, concordance of ctDNA and tumor findings, and evolution of genomic profile with treatment upon serial samples. Genomic DNA will be used for the determination of somatic changes in the tumor and genomic variations that may affect the response. Since the ctDNA and biopsy analyses are performed exclusively for research purposes, the results will be used to increase the clinical experience to help move the field forward, but they will not be made available to patients.

4.1.7 Removal of Patients from the Study

Every effort within the bounds of safety and patient choice should be made to have each patient complete the treatment period of the study. Patients who have treatment discontinued due to PD may be treated with any additional therapy deemed appropriate by the investigator. Patients with disease progression per RECIST can continue on therapy for clinical benefit if deemed appropriate by the investigator.

Patients may be discontinued from the study for any of the following reasons:

- Investigator recommends discontinuation and documents the reason(s)
- There is a need for any treatment not allowed by the protocol
- Patient's decision to withdraw consent or discontinue for any reason
- There is an unacceptable AE thought to be related to study medication

Any patient who discontinues during the treatment period should return to complete safety and disease assessments (see **Appendix A: Schedule of Assessments**).

4.1.8 COVID-19 Pandemic Study Procedures

During the COVID-19 pandemic, alternative methods for conducting study assessments should be considered when compliance, feasibility, and safety could be assured. These methods may include telemedicine visits (e.g., via telephone/video using compliant video-conference tools as permitted by health authority regulations) and use of primary care centers and local laboratories for blood draws and imaging/radiographs.

If alternative methods are used, local laboratory reference ranges will be documented. Local laboratory test results, laboratory accreditation, and reports of tumor assessments should be retrieved and documented in the patient's study records. The principal investigator (PI)/treating physician will review labs, determine clinical significance and sign/date results.

The use of remote consenting to obtain informed consent from clinical trial participants using paper or electronic consent forms is allowed in this study.

5 STUDY POPULATION

5.1 Patient Population

The study population will consist of subjects with selected HR+ (ER+ or/and PR+) advanced or metastatic solid tumors with PI3K (*PIK3CA, PIK3R1*) and/or *PTEN* alterations. Patients must have no available standard therapy known to prolong survival or are not candidates for such a therapy.

[redacted]

all patients complete the first 28 days, the study will advance to Part 2 (dose expansion), provided there is no more than 1 DLT observed. Patients will be considered evaluable for Part 1 once they have completed at least 1 cycle of treatment or they experience DLTs in the first treatment cycle.

[redacted]

Cohort 1: Ovarian cancer (ER+ and/or PR+, PI3K or PTEN altered).

Cohort 2: Endometrial cancer (ER+ and/or PR+, PI3K or PTEN altered).

Cohort 3: Breast cancer (ER+ and/or PR+, PI3K or PTEN altered). Cohort 3 will be enriched to include at least 7 patients naïve to any PI3Ki in Stage 1 and also in Stage 2.

Patients will be considered evaluable for Part 2 once they have completed at least 2 cycles of treatment and have at least one efficacy assessment.

[redacted]

5.3 Inclusion Criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

1. Histologically confirmed ER+ and/or PR+ advanced or metastatic solid cancer including ovarian cancer (cohort 1), endometrial cancer (cohort 2), or breast cancer (cohort 3). Cohort 3 will be enriched to include at least 7 patients naïve to any PI3Ki in Stage 1 and also in Stage 2. ER and/or PR positivity is defined as >10% immunohistochemical staining of any intensity.
2. Presence of one or more PI3K and/or PTEN alterations in tumor tissue. Genetic alterations will include *PIK3CA* gain of function mutations, *PIK3R1* loss of function mutations, *PTEN* loss of function mutations, and *PTEN* deletions.
3. Measurable disease per RECIST 1.1.
4. The patient (or legally acceptable representative, if applicable) provides written informed consent for the study.
5. Female or male ≥18 years of age on the day of informed consent signing.

6. Patients have no available standard therapy known to prolong survival. For cohort 3 prior treatment with a PI3Ki and everolimus is not required. The patients with or without prior treatment with PI3Ki and everolimus will qualify for enrollment
7. Adequate archived tumor tissue for the analysis for PI3K and PTEN alterations if available.
8. ECOG performance status of ≤2.
9. Adequate organ and marrow function as defined below:
    a. Hemoglobin ≥9.0 g/dL
    b. Absolute neutrophil count ≥1.5 × 10^9/L
    c. Platelet count ≥100 × 10^9/L
    d. TB ≤1.5 × institutional ULN; Patients with known Gilbert's disease who have TB ≤3 × ULN may be enrolled)
    e. AST/ ALT ≤3 × ULN. If patient has liver metastases, AST and ALT ≤5.0 × ULN.
    f. Creatinine ≤1.5 x ULN
    g. International normalized ratio ≤1.5.
10. Fasting blood glucose ≤140 mg/dL and hemoglobin A1c ≤8.5% (both criteria have to be met).
11. Cardiac ejection fraction ≥45%.
12. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 14 days prior to the initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Women of childbearing potential (WOCBP) must agree and commit to the use of 2 highly effective methods of birth control throughout the duration of the study until at least 4 months following the last dose of study drug. Acceptable methods are defined as those that result, alone or in combination, in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. Women using systemically acting hormonal contraceptives should add a barrier method. In certain countries (if permitted by law), WOCBP may agree to abide by heterosexual sexual abstinence during the time of participation in this study.
13. Male patients and their female partners of childbearing potential must agree and commit to use a barrier contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until at least 60 days following the last dose of study drug, in addition to their female partners using either an intrauterine device or hormonal contraception and continuing until at least 4 months following the last dose of study drug. This criterion may be waived for male patients who have had a vasectomy > 6 months before signing the ICF.
14. Willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations.

5.4 Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

1. The patient has CNS involvement. If the patient fulfills the following 3 criteria, she/he is eligible for the study:
    a. Completed prior therapy (including radiation and/or surgery) for CNS metastases, and
    b. CNS tumor is radiologically stable for ≥28 days prior to study start, and
    c. The patient is not receiving steroids and enzyme-inducing antiepileptic medications for brain metastases.
2. Patients with HER2 positive breast cancer.
3. Patients must be ≥4 weeks or at least 5 half-lives beyond treatment with any chemotherapy or other investigational therapy including hormonal, biological, or targeted agents at the time of treatment initiation.
    - NOTE: If the patient received major surgery, she/he must have recovered adequately from the toxicity and/or complications from the intervention prior to starting the study treatment.
4. For cohorts 1 and 2 prior treatment with fulvestrant or any PI3Ki.
5. Known hypersensitivity to copanlisib or fulvestrant, or any of the excipients of copanlisib or fulvestrant.
6. Concomitant use of strong CYP3A4 inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) or inhibitors (e.g., ritonavir, saquinavir, nelfinavir, boceprevir, telaprevir, ketoconazole, omeprazole). Use of strong inhibitors and/or inducers of CYP3A4 is not permitted from Day -14 of Cycle 1 until the end of the study treatment. (See **Appendix F:** Strong Inhibitors or Strong Inducers of CYP3A4)
7. The patient is currently receiving warfarin or other coumarin derived anticoagulants for treatment, prophylaxis, or otherwise. Therapy with heparin, low molecular weight heparin, fondaparinux, or direct oral anticoagulants such as rivaroxaban or apixaban is allowed.
8. Known additional malignancy that is progressing or requires active treatment.
9. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
10. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
11. Known history of human immunodeficiency virus infection.
12. History or current symptomatic pneumonitis.
13. Has clinically significant, uncontrolled heart disease and/or recent cardiac events, including any of the following:

a. History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
b. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
c. Documented cardiomyopathy
d. History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months
e. Uncontrolled hypertension defined by a systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg, with or without antihypertensive medication over the course of one clinic visit at intervals of ≥30 minutes. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.

14. Type 1 diabetes mellitus.
15. Uncontrolled type 2 diabetes mellitus.
16. Positive cytomegalovirus (CMV) polymerase chain reaction (PCR) test at baseline.
17. Active hepatitis B virus (HBV; chronic or acute; defined as having a known positive hepatitis B surface antigen [HbsAg] test at the time of screening) or hepatitis C infection requiring treatment.
    - Participants with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HbcAb] and absence of HbsAg) are eligible if HBV DNA is negative.
    - Participants with positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.

6 STUDY TREATMENT

[redacted]

consent, or discontinuation from the study treatment for any other reason. Patients who develop disease progression as centrally assessed according to the RECIST v1.1 criteria, as appropriate, may be allowed to continue treatment if the patient is benefitting from the study treatment in the opinion of the investigator, the patient is clinically asymptomatic, and continued study treatment is approved by the sponsor.

Dose escalation will not be allowed for progressive disease.

6.1.1 Copanlisib dosing requirements for pre-dose glucose levels

Copanlisib should be administered if pre-glucose level is <160 mg/dL for fasting, or <200 mg/dL for non-fasting participants. Fasting status refers to a $\geq$ 8 hours fast. Non-fasting status includes any caloric intake, such as meals, as well as juice, snacks, and other caloric intake not consistently called a meal.

For diabetic participants, who take insulin treatment at any cycle visit, timing and content of meal intake will be managed by the investigator. Consultation with treating physician or endocrinologist is advised.

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions may be associated with temporary increase in blood glucose. Addition of a meal in close proximity to copanlisib infusion may exacerbate glucose increase.

On infusion days, a low calorie or low carbohydrate diet is recommended. The timing and content of caloric meal intake and additional glucose testing (if clinically indicated) is managed and monitored by the investigators based on glucose response patterns during prior intervention days. Consultation with endocrinologist is advised**.**

All glucose measurements done at the site, oral glucose lowering medication and/or insulin administration, if applicable, fasting/non-fasting status and meal intake timing on infusion days will be collected as part of the clinical source documentation.

6.2 Dose Modification

Any toxicity observed during the study can be managed by interruption of the dose of study treatments or dose reductions. Repeated dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. Where toxicity recurs following re-challenge with study drugs, and where further dose interruption is considered inadequate for toxicity management, then withdrawal is indicated.

If either of the study drugs or both drugs need to be held due to AEs, then the study drug deemed to be responsible for the AE will be held until AE resolves to grade 1 or baseline. When copanlisib or fulvestrant dosing is interrupted, either the patient must recover completely, or the toxicity must revert to NCI CTCAE ≤Grade 1 or baseline before restarting study treatment. Patients whose NCI CTCAE Grade 3 or 4 event does not resolve to ≤1Grade or baseline within 4 weeks should be withdrawn from the study. When a patient withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed until ≤Grade 1 or baseline.

[redacted]

6.3 Toxicity Management

All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification. For dose modification, the investigator must first assess if the toxicity is considered at least possibly related to the study treatment and must then apply the dose modification guidelines accordingly. Below are dose delay and management tables for the study drugs. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study chair is recommended.

6.3.1 Copanlisib toxicity management

Table 5: Management of Nausea/vomiting

Toxicity	**Action to be Taken**
CTCAE Grade 1	No change in dose
CTCAE Grade 2	Hold* until ≤Grade 1. No change in dose
CTCAE Grade 3	Hold* until ≤Grade 2. Resume at one dose level lower, if indicated.**
CTCAE Grade 4	Off copanlisib treatment
*Patients requiring a delay of >2 weeks may go off protocol therapy. **Patients requiring >2 dose reductions should go off protocol therapy.	
Recommended management: Antiemetics	

Table 6: Management of Diarrhea

Toxicity	**Action to be Taken**
CTCAE Grade 1	No change in dose
CTCAE Grade 2	Hold* until ≤Grade 1. No change in dose
CTCAE Grade 3	Hold* until ≤Grade 2. Resume at one dose level lower, if indicated.**
CTCAE Grade 4	Off copanlisib treatment
*Patients requiring a delay of >2 weeks may go off protocol therapy. **Patients requiring >2 dose reductions should go off protocol therapy.	

Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at the first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Table 7: Management of thrombocytopenia

Toxicity	**Action to be Taken**
CTCAE Grade 1	No change in dose
CTCAE Grade 2	No change in dose
CTCAE Grade 3	Hold* until ≤Grade 1. Resume at one dose level lower, if indicated. **
CTCAE Grade 4	Off copanlisib treatment
*Patients requiring a delay of >2 weeks may go off protocol therapy. **Patients requiring >2 dose reductions should go off protocol therapy.	

Table 8: Management of Neutropenia

Toxicity	**Action to be Taken**
CTCAE Grade 1	No change in dose
CTCAE Grade 2	No change in dose
CTCAE Grade 3	Hold* until ≤Grade 2. Resume at one dose level lower, if indicated.**
CTCAE Grade 4	Off copanlisib treatment
*Patients requiring a delay of >2 weeks may go off protocol therapy. **Patients requiring >2 dose reductions should go off protocol therapy.	

6.3.1.1 Dose Modification Rules for Transient Post-Infusion Hyperglycemia

Patients who develop transient post-infusion glucose >250 mg/dL after study drug 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). Guidelines for the management of transient glucose increases are given in the tables below. The continuing occurrence of post-infusion blood glucose >500 mg/dL, based on repeated laboratory analysis despite optimal glucose-lowering therapy after 2 infusions of copanlisib, will require dose reduction by one dose level.

- Further dose reduction (where appropriate per study design/population) is allowed as long as discontinuation criteria were not met.
- Dose re-escalation is allowed when a patient has achieved controlled glucose levels per investigator's judgment.

- Persistent occurrence of post-infusion blood glucose >500 mg/dL based on laboratory analysis, which occurred at the lowest dose level despite optimal glucose-lowering therapy (after at least one cycle of treatment) with the consultation of a diabetes specialist requires permanent discontinuation of the study drug.

Table 9: Management of post-infusion glucose increase

Toxicity	**Action to be Taken**
Glucose increase of CTCAE Grade 1 (abnormal glucose level above baseline with no medical intervention)	• Continue study treatment
Glucose increase of CTCAE Grade 2 (change in daily management, from baseline for a diabetic; oral antiglycemic agent is initiated; workup for diabetes)	• Hydration as clinically indicated • When planning next infusion prophylaxis with oral glucose-lowering medication per local SOC is recommended • Consultation with an endocrinologist for diabetic patients is recommended
Glucose increase of CTCAE ≥Grade 3 (insulin therapy initiated; hospitalization or urgent intervention indicated; life-threatening consequences)	• Hydration as clinically indicated (orally, IV) • Insulin therapy per local SOC • When planning next infusion consider prophylaxis with oral glucose-lowering medication per local SOC • Consultation with an endocrinologist is recommended

Table 10: Management of Transient Glucose Increase on the Day of Copanlisib Infusion

Criteria	**Recommendations**
Asymptomatic glucose increases to a value ≤250 mg/dL	• Does not generally require treatment with glucose-lowering medication.
Asymptomatic glucose increases to a value >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 treatment if hydration status is normal as clinically assessed. • Consultation with an endocrinologist is recommended. • Hydration, if appropriate.

	• When planning the next infusion, consider prophylaxis with oral glucose-lowering medication.
Symptomatic or persisting glucose increases to a value >250 mg/dL	• Hydration status should be clinically assessed. • If the clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory tests confirming increase should be repeated. If the repeated glucose value is persistent and/or the patient is symptomatic and/or the hydration status indicates the need for hydration, glucose-lowering medication should be administered. • Prompt input from a diabetes specialist should be obtained. • Hydration if appropriate • Rapid/short-acting insulin may be given for glucose persisting at >250 mg/dL or if the patient is symptomatic during the infusion day. • Rapid/short-acting insulin. • According to the institution sliding scale coverage of glucose persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate. When planning the next infusion, consider prophylaxis with oral glucose-lowering medication.

Table 11: Management of Transient Glucose Increase on Subsequent Days Following Copanlisib Infusion

Criteria	**Recommendations**
Grade 2 Max post infusion glucose >200 mg/dL noted on subsequent days	• Oral glucose-lowering medication recommended on subsequent days. • Consultation with an endocrinologist is recommended. • The use of sulphonylurea/metaglinides, insulin

	secretagogues medications to manage increased glucose levels post drug infusions is not recommended. • Treatment with glucose-lowering medication suggested according to the local standards of practice. •

The need for glucose monitoring at home should be determined by the investigator based on the post-infusion glucose profile and clinical status of the patient.

6.3.1.2 Monitoring of diabetic patients

If the patient already monitors his/her blood glucose as part of routine anti-diabetic care, the routine measurements should not be replaced by the study-specific measurements.

6.3.1.3 Management 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 BP increases following copanlisib will need to be individualized for each patient, but experience from a Bayer-sponsored phase 1 study with copanlisib 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 and moderate inhibitors of CYP3A4) should be used with caution due to a potential CYP3A4 interaction. In general, it is advisable for investigative teams to be prepared, so that anti-hypertensive medication is readily available in case of need.

In the event of the occurrence of arterial hypertension ≥150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested as indicated in the Dose Modification of Copanlisib for Arterial Hypertension **Table 13** below. In the event of the occurrence of grade 3 arterial hypertension (≥160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted, and anti-hypertensive treatment, as suggested above, is administered. The infusion can be resumed when BP has returned to <150/90 mmHg.

Table 12: Management of Blood Pressure

Toxicity (CTCAE)	**Study Drug action**	**Recommendation**
Pre-dose measurements BP ≥150/90 mmHg	No dose should be given until recovery to <150/90 mmHg	Consider 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 doesn't return to <150/90 mmHg, delay dosing until the next visit.
During infusion: CTCAE hypertension of grade 3 or ≥160/100 mmHg	The infusion can be interrupted or slowed down, and the administration of BP-lowering therapy should be initiated.	The infusion may be resumed when BP has returned to <150/90 mmHg at the investigator's discretion or skipped. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion[a].
Post-dose: Drug-related CTCAE hypertension of grade 3 or ≥160/100 mmHg[b]		Administration of BP-lowering therapy should be initiated according to the local SOC. Additional measurements to be performed as clinically indicated until recovery to <150/90 mmHg. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion[b].
CTCAE hypertension of grade 4	Permanent discontinuation	
[a]: The lowest dose level is 45 mg. [b]: Not manageable despite optimal antihypertensive treatment.		

6.3.1.3.1 Blood pressure measurement on treatment days

BP will be measured every 5-10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results <150/90 mmHg. If BP is ≥150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of the study drug. The patient should rest for 5-10 min before BP is recorded.

On infusion days, BP will be measured at 0 hour (pre-dose), 30 minutes (mid-infusion), 60 minutes (end of infusion), and 1 hour after the end of infusion

NOTE: A window of ±10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement.

6.3.1.4 Dermatologic toxicity

The recommendations for dose modifications in cases of dermatologic toxicity are outlined in **Table 14**. If these recommendations are not followed, the rationale for other measures will be documented in detail in the participant's medical record.

Table 13: Dose modification of copanlisib for dermatologic toxicity

Toxicity (CTCAE grade)	**Occurrence**	**For current course of therapy**	**For next course of therapy**
Grade 1 and 2	Any appearance	No change	No change
Grade 3 [a]	1st appearance	Interruption until Grade ≤2	Decrease by one dose level [b]
	2nd appearance	Interruption until Grade ≤2	Decrease by one dose level [b]
	3rd appearance	Permanent discontinuation	–
Grade 4	1st appearance	Permanent discontinuation	–

Abbr.: CTCAE = Common terminology criteria of adverse events.

a. Despite maximum supportive therapy.

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

If dermatologic changes occur, the participant should be treated quickly and aggressively. **Table 15** can be used as guidance.

Table 14: 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 b.i.d. or Minocycline 100 mg b.i.d.
Nail Changes	Moisturizers
Pruritus	Pramoxine 1% cream or Sarna Ultra Cream
MODERATE (CTCAE Grade 2)	
Dry Skin / Fissures	Emollients and topical as above plus Ammonium lactate or Urea 20%
Rash	Topical hydrocortisone 2.5% and/or clindamycin 1% gel plus doxycycline 100 mg b.i.d. or Minocycline 100 mg b.i.d.
Nail Changes	Vinegar soaks (dilute 1:1 white vinegar in water and soak fingers for 10 min 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
Nail Changes	Topical antibacterial / antifungal (ciclopirox) cream or Topical high potency steroids (clobetasol ointment) Consider dermatology consult for nail avulsion
Pruritus	Pregabalin 50-100 mg b.i.d.

Abbr.: b.i.d. = Twice daily, CTCAE = Common terminology criteria for adverse events.

6.3.1.5 Management of Infections

Serious, including fatal, infections occurred in 8.9% of 558 patients treated with copanlisib monotherapy. The most common serious infection was pneumonia. Monitor patients for signs and symptoms of infection and withhold copanlisib for Grade 3 and higher infection.

Serious pneumocystis jiroveci pneumonia (PJP) occurred in 0.9% of 558 patients treated with copanlisib monotherapy. Before initiating treatment with copanlisib, consider PJP prophylaxis for populations at risk. Withhold copanlisib in patients with suspected PJP infection of any grade. If confirmed, treat infection until resolution, then resume copanlisib at previous dose with concomitant PJP prophylaxis

6.3.1.6 Management of Non-Infectious Pneumonitis

The investigator is requested to differentiate between non-infectious pneumonitis, and infectious pneumonitis (viral, bacterial, or 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".

In the event of suspected non-infectious pneumonitis, modify copanlisib treatment as per **Table 16** below.

Table 15: Management of Non-Infectious Pneumonitis

Suspected or confirmed NIP per CTCAE	**Action taken**	**Re-treatment dose after recovery**
Grade 1	No Change	N/A
Grade 2	Dose Interruption Until recovery to ≤Grade 1	Decrease dose to the next lowest dose level[a].
Grade 2 second re-occurrence	Permanent Discontinuation	N/A
Grade 3	Permanent discontinuation	N/A
Grade 4	Permanent discontinuation	N/A
NA = Not applicable; NIP = Non-infectious pneumonitis; [a]: Not applicable for 45 mg dose level. No re-escalation is allowed after the dose reduction. The lowest dose level is 45 mg; if a patient is already on the 45 mg dose level and cannot tolerate treatment study treatment will be discontinued permanently.		

6.3.2 Fulvestrant toxicity management

6.3.2.1 Management of Hepatic Impairment

A Fulvestrant dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered IM into the buttock slowly (1 - 2 minutes) as one 5 mL injection on Day 1 and Day 15 of the first and Day 1 of each subsequent 28-day cycle. Fulvestrant has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).

6.3.3 Other toxicities

Other toxicities that are not clearly attributable to copanlisib or fulvestrant, including overlapping toxicities, should be initially managed as follows:

- Treatment interruption or dose modification for Grade 1 or grade 2 AEs per CTCAE would be implemented at the investigator and patient's discretion.
- Both agents should be interrupted for Grade 3 AEs per CTCAE until the AEs have reached grade 1 or have returned to baseline. Following the resolution of toxicity, copanlisib may be resumed at the same dose level or at one or more dose levels lower, at the investigator's discretion. Fulvestrant should be resumed at the same dose level. Sequential reintroduction of each agent should be considered if clinically appropriate.
- Both agents should be interrupted for Grade 4 AEs per CTCAE until the AEs have reached grade 1 or have returned to baseline. For AEs that are not life-threatening and that can

be managed, treatment with copanlisib may be resumed at a lower dose level, but fulvestrant should be resumed at the same dose level. Otherwise, patients must discontinue treatment. Sequential reintroduction of each agent should be considered if clinically appropriate.

6.3.4 COVID-19/SARS-CoV-2 Infection

The following guidelines apply to patients with confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection:

- For patients with active SARS-CoV-2 infection, study treatment should be delayed for at least 14 days from the first positive COVID-19 test or start of symptoms, whichever is later.
- Prior to restarting study treatment, patients should be afebrile for 72 hours and SARS-CoV-2-related symptoms should have recovered to Grade ≤1 for a minimum of 72 hours. The sponsor should be informed when study treatment is resumed.

The sponsor and/or the supporting company must be informed within 24 hours of awareness of a patient with COVID-19/ SARS-CoV-2 infection.

6.4 Concomitant Therapy

All medications that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment -including all prescription, over-the-counter, IV medications and fluids, supportive care drugs and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions- will be captured in the electronic medical record (EMR), but not in the electronic case report forms (eCRF).

6.4.1 Prohibited Medications/Therapies

Use of the following concomitant medications/therapies is prohibited during the study:

- Any chemotherapy, radiation therapy, immunotherapy, hormone, or biologic therapy for cancer treatment other than that under investigation in this study.
  Exceptions include the following:
  - Palliative radiotherapy is allowed during the study if the patient is otherwise benefitting from the study treatment in the opinion of the investigator. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 28 days as long as any bone marrow toxicity has recovered.

[redacted]

- Concomitant use of herbal preparations containing CYP3A4 inducers (e.g. St John's Wort) is not permitted during the study.
- Grapefruit and grapefruit juice (a CYP3A4 inhibitor) consumption is not permitted during the study.
- **The use of systemic corticosteroids or immunosuppressants after starting the study intervention should be avoided, except:**
    - (1) If a participant is on chronic corticosteroid therapy, e.g. replacement therapy such as physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency (in dosing not exceeding 10 mg daily of prednisone equivalent) is not considered a form of systemic treatment.
    - (2) Systemic corticosteroids above 10 mg prednisolone or equivalent or other immunosuppressants may be allowed after starting the study intervention for the management of acute conditions (e.g. treatment of non-infectious pneumonitis) or as premedication for radiological contrast infusion as clinically indicated.

  Participants may be using inhaled or topical steroids. For more information about steroid use in management of skin toxicities, please refer to **6.3.1.4**.

If treatment with a prohibited medication/therapy is necessary, the patient will be withdrawn from the study after discussion with the sponsor.

6.4.2 Potential Drug Interactions

[redacted]

No drug-drug interaction (DDI) effect of copanlisib on fulvestrant metabolism is expected, because copanlisib is not an inhibitor or inducer of drug metabolizing enzymes involved in fulvestrant metabolism, and vice versa.

6.5 Supportive Care

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

Gastrointestinal Disorders

Nausea, vomiting, and diarrhea have been very common in patients treated with copanlisib. Patients with these side effects may require supportive care, including antiemetics, antidiarrheal medications, and IV fluids. Patients should receive appropriate antiemetic treatment at the first onset of nausea or vomiting in accordance with local practice guidelines. As per international guidance on antiemetic use in cancer patients (European Society for Medical Oncology, National Comprehensive Cancer Network), generally, a single-agent antiemetic should be considered (e.g., dopamine receptor antagonist, antihistamine, or dexamethasone).

Fatigue

Fatigue has been very common in patients treated with copanlisib. Patients with fatigue may require symptomatic management as needed.

Hematological Disorders

Patients with anemia and/or thrombocytopenia may require supportive care, including transfusion of red blood cells and platelets and administration of hematological growth factors.

Metabolism abnormalities

Hypophosphatemia has occurred in patients treated with copanlisib. Phosphate replacement might be needed.

Hyperglycemia

Hyperglycemia has been very common in patients treated with copanlisib. Hydration and/or oral glucose-lowering medication or insulin might be needed depending on the severity of the blood glucose level and the study treatment stage.

Vascular Disorders

Hypertension (includes secondary hypertension) has been frequent in patients treated with copanlisib. Anti-hypertensive treatment might be needed to manage hypertension.

Infections

Lower respiratory tract infections have been very common in patients treated with copanlisib. Infections need to be treated until resolution before resuming the treatment with copanlisib.

6.6 Contraception

Both copanlisib and fulvestrant can cause fetal harm during embryonic development. In pregnant animal models, the administration of copanlisib or fulvestrant caused embryo-fetal death and fetal abnormalities. No information is available on the safety of copanlisib or fulvestrant in pregnant human females. Neither copanlisib nor fulvestrant should be administered to pregnant

women. Female patients of childbearing potential must either abstain from heterosexual intercourse or use a highly effective method of contraception for the course of the study through 150 days after the last dose of copanlisib or fulvestrant. Males with female partners of reproductive potential must abstain from sexual intercourse. Alternatively, they and their partners must use a highly effective method of contraception when engaging in sexual intercourse for the course of the study through 90 days after the last dose of copanlisib or fulvestrant.

Patients should be informed that taking the study medications may involve unknown risks to the fetus (unborn baby) if the pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement for the duration of the study and after the last day of treatment as described in the paragraph above. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.6.1 Female Patients

Women in the following categories are not considered women of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented tubal ligation
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal female
  Postmenopausal is defined as ≥45 years of age, with at least 12 months of spontaneous amenorrhea.

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly, as described in **Table 17** during the protocol-defined timeframe.

Table16: Highly Effective Contraception Methods

• Combined (estrogen and progestogen-containing) hormonal contraception
  ○ Oral
  ○ Intravaginal
  ○ Transdermal

• Progestogen-only hormonal contraception
  ○ Oral
  ○ Injectable
  ○ Implantable

• Intrauterine devices and intrauterine hormone-releasing system
• Bilateral tubal occlusion (women)

• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence (men and women) Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient. Periodic abstinence (such as a calendar, symptothermal and post-ovulation methods, withdrawal (coitus interruptus), and the lactational amenorrhea method are not acceptable methods of contraception

6.6.2 Male Patients

Male patients of childbearing potential must use a male condom plus spermicide. In addition, if the male patient's female partner is of childbearing potential, she should use a highly effective contraception method, as described in **Table 17**.

6.7 Use in Pregnancy

If a patient inadvertently becomes pregnant while on study treatment, the patient will immediately be removed from the study. The investigative team will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The investigator must notify the sponsor and/or supporting company within 24 hours of awareness of any pregnancy occurring from study treatment initiation until 150 days after the last dose of study treatment. The outcome of the pregnancy will be reported to the sponsor and/or supporting company without delay and within 24 hours. Individual cases with an abnormal outcome such as death, abortion, congenital anomaly, or other disabling or life-threatening complications to the mother or newborn are considered as SAEs and should be reported using the SAE form. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor and the supporting company. If a male patient impregnates his female partner during the study or in 90 days after the last dose of the study treatment, the investigative team must be informed immediately, and the pregnancy reported to the sponsor and/or the supporting company. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor and/or supporting company.

6.8 Use in Nursing Women

It is not known if copanlisib, fulvestrant or their metabolites are excreted in human milk. Copanlisib and fulvestrant can be detected in rat milk if administered to lactating animals. Since

many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breastfeeding are not eligible for enrollment.

6.9 Patient Withdrawal/Discontinuation Criteria

Patients may withdraw consent at any time for any reason or be dropped from the study at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A patient must be discontinued from the study for any of the following reasons:

- The patient or legal representative withdraws consent. Every effort will be made to determine why any subject withdraws from the study prematurely.

A patient must be discontinued from study treatment (but may continue to be monitored in the study) for any of the following reasons:

- The patient or legal representative withdraws consent
- Confirmed radiographic disease progression with the exception of patients who are benefitting from the study treatment in the opinion of the investigator, the patient is clinically asymptomatic, and continuation of study treatment is approved by the sponsor.
- Unacceptable toxicity
- An intercurrent illness that prevents further administration of study treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum or urine pregnancy test
- Non-compliance with study treatment or procedure requirements
- Initiation of new anticancer therapy including another investigational agent
- The patient is lost to follow-up. A genuine effort must be made to determine the reason(s) why a patient fails to return for the necessary visits. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent requesting him/her to contact the clinic
- Death
- Dose interruption that exceeds 4 weeks
- Administrative reasons

When a patient is permanently discontinued from receiving study treatment prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. The patient will continue to be followed for safety unless consent is withdrawn or the patient is lost to follow-up or initiation of a new anticancer therapy. Patients who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until PD, death, initiation of new anticancer therapy, withdrawal of consent,

or lost to follow-up. After confirmed disease progression, each patient will be followed for survival status until death, withdrawal of consent, or lost to follow-up.

6.10 Length and End of Study

The study begins when the first patient signs the ICF. Patients will receive study treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study treatment for any other reason. There is no maximum number of cycles a patient may receive if, in the opinion of the investigator, the patient is benefiting clinically from the study treatment.

The overall end of the study is defined as the time point when the final analysis is completed after the data collection stops in all cohorts, Also, the investigator may decide to terminate the study at any time.

7 ASSESSMENT OF SAFETY

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the sponsor, the FDA, and the institutional review board (IRB) in accordance with 21 Code of Federal Regulations (CFR) 312.32.

7.1 Safety Parameters

7.1.1 Definition of Adverse Event

The International Council on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6 defines an AE as “any untoward medical occurrence in a patient, or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient’s preexisting condition. An abnormal laboratory finding that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

AEs may be treatment-emergent (i.e., occurring after initial receipt of investigational product) or non-treatment-emergent. A non−treatment-emergent AE is any new sign or symptom, disease, or other untoward medical events that begin after the written informed consent has been obtained, but before the patient has received the investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled in the study) for a documented preexisting condition, that did not worsen from baseline, is not considered an AE (serious or non-serious). An untoward medical

event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both SAEs and non-serious AEs.

7.1.2 Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., screening, run-in, treatment, and wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in the offspring of the patient
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2 Adverse Event Reporting Period

All AEs, SAEs, and other reportable safety events that occur after the ICF is signed but before study treatment initiation must be reported by the investigator if the event causes the patient to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- The investigator must report all AEs from the time of first protocol-specific intervention through 30 days following cessation of study treatment.
- All AEs meeting serious criteria from the time of first protocol-specific intervention through 30 days following cessation of study treatment or before the initiation of a new anticancer therapy, whichever comes first, must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the period specified above must be reported immediately by the investigator if the event is considered related to the study treatment. These events must be followed until they are resolved or stabilized

Information to be reported in the description of each AE includes:

- AE (verbatim)
- Severity grade (CTCAE Grade 1–5)
- The date of onset and resolution of the AE
- Whether the AE is serious or not, where an SAE is defined as in Section **7.1.2**.
- Investigator causality assessment with respect to the study treatment (yes or no)
- Action taken with respect to the study treatment (none, temporarily interrupted, dose reduced, permanently discontinued, unknown, not applicable)

- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

7.3 Assessment of Adverse Events

All AEs and SAEs, whether reported by the patient, discovered by study personnel during questioning, or detected through a physical exam, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study treatment (see following guidance), and actions taken.

AE Attribution:

The investigator (or physician designee) is responsible for verifying and providing source documentation for all AEs and assigning the attribution for all AEs for patients enrolled.

Attribution: The determination of whether an AE is related to a medical treatment or procedure.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Definite - the AE is clearly related to the investigational agent.

Probable - the AE is likely related to the investigational agent.

Possible - the AE may be related to the investigational agent.

Unlikely - The AE is doubtfully related to the investigational agent.

Unrelated - The AE is clearly NOT related to the investigational agent.

Expected AEs are those AEs that are listed or characterized in the current United States Product Insert.

Unexpected AEs are those not listed in the current IB or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the IB.

7.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.4.1 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points.

7.4.2 Specific Instructions for Recording Adverse Events

AEs and SAEs will be recorded in the Molecular and Clinical Data Integrated Platform (MOCLIP).

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Colloquialisms and abbreviations should be avoided.

This study will follow the NCI Recommended AE Recording Guidelines for Phase II studies, as per the below **Table 17**.

Table 17: Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.4.2.1 Diagnosis Versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Death of unknown cause".

7.4.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the study and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is essential to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.4.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions that were planned prior to the start of the safety reporting period
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

7.5 Assessment of Severity of Adverse Events

The severity of the AEs will be graded according to the **NCI CTCAE V.5.0.** Events not included in the NCI CTCAE will be scored as follows:

General grading:

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first-line treatment.

- **Grade 4:** Life-threatening: discomfort that represents an immediate risk of death

7.6 Serious Adverse Event Reporting Requirements for MDACC Sponsor Single Site Investigational New Drug (IND) Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
- Important medical events, as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the PI or the IND sponsor, MDACC IND office.
- All events occurring during the conduct of a protocol and meeting the definition of an SAE must be reported to the IRB following the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- SAEs will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of the drug or protocol-specific timeline, unless the participant withdraws consent.
- SAEs must be followed until clinical recovery is complete, and laboratory tests have returned to baseline, the progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND office within 5 working days of knowledge of the event regardless of the attribution.
- Death or life-threatening events that are unexpected, possibly, probably, or definitely related to the study treatment must be reported (initial or follow up) to the IND office within 24 hours of knowledge of the event.
- Additionally, any SAEs that occur after the 30-day time period or protocol-specific timeline that is related to the study treatment must be reported to the IND office. This may include the development of a secondary malignancy.

- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND office and MDACC IRB.
- All events reported to the supporting company must also be reported to the IND office.

Reporting to the FDA:

- Serious Adverse Events will be forwarded to the FDA by the IND sponsor (MDACC IND office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious AEs are reported according to the CFR, GCP, protocol guidelines, sponsor's guidelines, and IRB policy.

[redacted]

7.7.1 Overdose

Overdose includes only clinically symptomatic doses that are at least twice the intended dose. Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved study drugs) must be communicated to the sponsor and supporting company within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

[redacted]

[redacted]

Cohort 1: Ovarian cancer (ER+ and/or PR+, PI3K or PTEN altered)

Cohort 2: Endometrial cancer (ER+ and/or PR+, PI3K or PTEN altered)

Cohort 3: Breast cancers (ER+ and/or PR+, PI3K or PTEN altered). This cohort will be enriched to include at least 7 patients naïve to any PI3Ki in Stage 1 and in Stage 2.

[redacted]

[redacted]

[redacted]

8.1 Safety Analysis

All patients who received at least 1 dose of both copanlisib and fulvestrant will be included in a descriptive safety analysis. The safety profiles will be assessed through summaries of AEs, serious AEs, AEs leading to treatment discontinuation, and treatment-related death. The safety analysis will report the frequency, severity, and duration of all treatment related AEs and laboratory abnormalities, dose interruptions, dose reductions, and toxicity-related treatment discontinuation. The worst per-patient toxicity according to NCI CTCAE grade will be used. The Bayesian Beta-Binomial model will be used to quantify the statistical inference of AE rates.

The **MDACC IND Office Medical and Safety Group** will be provided with a copy of the safety and efficacy analysis when available.

8.1.1 Clinical Laboratory Analyses

All clinical laboratory values will be listed individually and tabulated in a manner to identify safety concerns on a per-patient basis. Listing tables will be prepared for each laboratory measure and will be structured to permit review of the patient data as they progress on treatment. The tables will list the cycle of treatment, copanlisib and fulvestrant doses for dose confirmation data, and the associated NCI CTCAE grade. Descriptive summary statistics will be generated per laboratory parameter.

Summary tables will be prepared to examine the distribution of these toxicities per cycle.

Graphic displays and shift tables may be provided to illustrate results over time on study. Assessment of cumulative toxicities may be made.

8.2 Efficacy Analysis

The ORR is defined as the proportion of patients who achieve CR or PR by the combination therapy per RECIST 1.1. Bayesian beta-binomial model and the CBHM will be used to model the data observed within each cohort. Bayesian 95% credible interval will be derived. Summary statistics will be given for secondary efficacy endpoints without borrowing information across cohorts. Time-to-event methodology will be used to assess mortality outcomes. Specifically, a log-rank statistic (accompanied by a Kaplan-Meier plot) will be the primary method of analysis for the mortality endpoint. Model-based methods (e.g., Cox proportional hazards or other robust methods) may also be applied.

8.3 Data Collection

8.3.1 Data Protection and Confidentiality

All patients who meet eligibility criteria and are enrolled in this study will be registered in Clinical Oncology Research e-Database (CORe) at MDACC. All study patients must be registered in the CORe. The date of the current ICF is displayed to ensure only the most current IRB-approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical study. The investigator must ensure that each study patient's anonymity will be maintained in accordance with applicable laws. The investigator should keep a separate log of identification numbers, names, and addresses. Documents that contain the names associated with these identification numbers (e.g., written consent/assent forms) should be maintained by the investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and applicable reporting (if any).

Protocol-specific data will be entered into MOCLIP/CORe (or other databases); MOCLIP/CORe (or other databases) will be used as the eCRF.

9 Ethical and regulatory requirements

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki. The study will comply with United States FDA regulations and applicable local, state, and federal laws. Details are described in the MD Anderson institutional standard operating procedures and policies.

10 REFERENCES

1. Andre F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Papai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D, Group S-S. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380(20):1929-40. Epub 2019/05/16. doi: 10.1056/NEJMoa1813904. PubMed PMID: 31091374.
2. Munoz J, Wheler J, Kurzrock R. Expression of estrogen and progesterone receptors across human malignancies: new therapeutic opportunities. Cancer Metastasis Rev. 2015;34(4):547-61. Epub 2014/12/30. doi: 10.1007/s10555-014-9543-z. PubMed PMID: 25543191.
3. Juric D, Janku F, Rodon J, Burris HA, Mayer IA, Schuler M, Seggewiss-Bernhardt R, Gil-Martin M, Middleton MR, Baselga J, Bootle D, Demanse D, Blumenstein L, Schumacher K, Huang A, Quadt C, Rugo HS. Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol. 2019;5(2):e184475. Epub 2018/12/14. doi: 10.1001/jamaoncol.2018.4475. PubMed PMID: 30543347; PMCID: PMC6439561.
4. Janku F G-LI, Wheler JJ, et al. . Screening for PIK3CA mutations, PTEN loss, and RAS/RAF mutations in early-phase protocols with PI3K/mTOR pathway inhibitors. J Clin Oncol. 2011;29(suppl):abstr 10507.
5. Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, Tsimberidou AM, Stepanek VM, Moulder SL, Lee JJ, Luthra R, Zinner RG, Broaddus RR, Wheler JJ, Kurzrock R. Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. Cell Rep. 2014;6(2):377-87. Epub 2014/01/21. doi: 10.1016/j.celrep.2013.12.035. PubMed PMID: 24440717; PMCID: PMC4409143.
6. Janku F, Lee JJ, Tsimberidou AM, Hong DS, Naing A, Falchook GS, Fu S, Luthra R, Garrido-Laguna I, Kurzrock R. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS One. 2011;6(7):e22769. Epub 2011/08/11. doi: 10.1371/journal.pone.0022769. PubMed PMID: 21829508; PMCID: PMC3146490.
7. Janku F, Wheler JJ, Naing A, Falchook GS, Hong DS, Stepanek VM, Fu S, Piha-Paul SA, Lee JJ, Luthra R, Tsimberidou AM, Kurzrock R. PIK3CA mutation H1047R is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors in early-phase clinical trials. Cancer Res. 2013;73(1):276-84. Epub 2012/10/16. doi: 10.1158/0008-5472.CAN-12-1726. PubMed PMID: 23066039; PMCID: PMC3537862.
8. Janku F, Wheler JJ, Westin SN, Moulder SL, Naing A, Tsimberidou AM, Fu S, Falchook GS, Hong DS, Garrido-Laguna I, Luthra R, Lee JJ, Lu KH, Kurzrock R. PI3K/AKT/mTOR inhibitors in patients with

breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol. 2012;30(8):777-82. Epub 2012/01/25. doi: 10.1200/JCO.2011.36.1196. PubMed PMID: 22271473; PMCID: PMC3295566.
9. Langdon SP, Gourley C, Gabra H, Stanley B. Endocrine therapy in epithelial ovarian cancer. Expert Rev Anticancer Ther. 2017;17(2):109-17. Epub 2016/12/15. doi: 10.1080/14737140.2017.1272414. PubMed PMID: 27967255.
10. Argenta PA, Thomas SG, Judson PL, Downs LS, Jr., Geller MA, Carson LF, Jonson AL, Ghebre R. A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. Gynecol Oncol. 2009;113(2):205-9. Epub 2009/02/26. doi: 10.1016/j.ygyno.2009.01.012. PubMed PMID: 19239974.
11. Ethier JL, Desautels DN, Amir E, MacKay H. Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. Gynecol Oncol. 2017;147(1):158-66. Epub 2017/07/12. doi: 10.1016/j.ygyno.2017.07.002. PubMed PMID: 28689667.
12. Ribeiro JR, Freiman RN. Estrogen signaling crosstalk: Implications for endocrine resistance in ovarian cancer. J Steroid Biochem Mol Biol. 2014;143:160-73. Epub 2014/02/26. doi: 10.1016/j.jsbmb.2014.02.010. PubMed PMID: 24565562; PMCID: PMC4127339.
13. Jerzak KJ, Duska L, MacKay HJ. Endocrine therapy in endometrial cancer: An old dog with new tricks. Gynecol Oncol. 2019;153(1):175-83. Epub 2019/01/09. doi: 10.1016/j.ygyno.2018.12.018. PubMed PMID: 30616900.
14. Slomovitz BM, Jiang Y, Yates MS, Soliman PT, Johnston T, Nowakowski M, Levenback C, Zhang Q, Ring K, Munsell MF, Gershenson DM, Lu KH, Coleman RL. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol. 2015;33(8):930-6. Epub 2015/01/28. doi: 10.1200/JCO.2014.58.3401. PubMed PMID: 25624430; PMCID: PMC4348638.
15. Wheler JJ, Moulder SL, Naing A, Janku F, Piha-Paul SA, Falchook GS, Zinner R, Tsimberidou AM, Fu S, Hong DS, Atkins JT, Yelensky R, Stephens PJ, Kurzrock R. Anastrozole and everolimus in advanced gynecologic and breast malignancies: activity and molecular alterations in the PI3K/AKT/mTOR pathway. Oncotarget. 2014;5(10):3029-38. Epub 2014/06/11. doi: 10.18632/oncotarget.1799. PubMed PMID: 24912489; PMCID: PMC4102789.
16. Chu Y, Yuan Y. A Bayesian basket trial design using a calibrated Bayesian hierarchical model. Clin Trials. 2018;15(2):149-58. Epub 2018/03/04. doi: 10.1177/1740774518755122. PubMed PMID: 29499621; PMCID: PMC5891374.
17. Voutsadakis IA. Hormone Receptors in Serous Ovarian Carcinoma: Prognosis, Pathogenesis, and Treatment Considerations. Clin Med Insights Oncol. 2016;10:17-25. Epub 2016/04/08. doi: 10.4137/CMO.S32813. PubMed PMID: 27053923; PMCID: PMC4814131.
18. Sieh W, Kobel M, Longacre TA, Bowtell DD, deFazio A, Goodman MT, Hogdall E, Deen S, Wentzensen N, Moysich KB, Brenton JD, Clarke BA, Menon U, Gilks CB, Kim A, Madore J, Fereday S, George J, Galletta L, Lurie G, Wilkens LR, Carney ME, Thompson PJ, Matsuno RK, Kjaer SK, Jensen A, Hogdall C, Kalli KR, Fridley BL, Keeney GL, Vierkant RA, Cunningham JM, Brinton LA, Yang HP, Sherman ME, Garcia-Closas M, Lissowska J, Odunsi K, Morrison C, Lele S, Bshara W, Sucheston L, Jimenez-Linan M, Driver K, Alsop J, Mack M, McGuire V, Rothstein JH, Rosen BP, Bernardini MQ, Mackay H, Oza A, Wozniak EL, Benjamin E, Gentry-Maharaj A, Gayther SA, Tinker AV, Prentice LM, Chow C, Anglesio MS, Johnatty SE, Chenevix-Trench G, Whittemore AS, Pharoah PD, Goode EL, Huntsman DG, Ramus SJ. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. Lancet Oncol. 2013;14(9):853-62. Epub 2013/07/13. doi: 10.1016/S1470-2045(13)70253-5. PubMed PMID: 23845225; PMCID: PMC4006367.
19. Hogdall EV, Christensen L, Hogdall CK, Blaakaer J, Gayther S, Jacobs IJ, Christensen IJ, Kjaer SK. Prognostic value of estrogen receptor and progesterone receptor tumor expression in Danish ovarian

cancer patients: from the 'MALOVA' ovarian cancer study. Oncol Rep. 2007;18(5):1051-9. Epub 2007/10/05. PubMed PMID: 17914554.
20. Burges A, Bruning A, Dannenmann C, Blankenstein T, Jeschke U, Shabani N, Friese K, Mylonas I. Prognostic significance of estrogen receptor alpha and beta expression in human serous carcinomas of the ovary. Arch Gynecol Obstet. 2010;281(3):511-7. Epub 2009/07/30. doi: 10.1007/s00404-009-1185-y. PubMed PMID: 19639330.
21. Liu JF, Hirsch MS, Lee H, Matulonis UA. Prognosis and hormone receptor status in older and younger patients with advanced-stage papillary serous ovarian carcinoma. Gynecol Oncol. 2009;115(3):401-6. Epub 2009/10/03. doi: 10.1016/j.ygyno.2009.08.023. PubMed PMID: 19796795.
22. Lee P, Rosen DG, Zhu C, Silva EG, Liu J. Expression of progesterone receptor is a favorable prognostic marker in ovarian cancer. Gynecol Oncol. 2005;96(3):671-7. Epub 2005/02/22. doi: 10.1016/j.ygyno.2004.11.010. PubMed PMID: 15721410.
23. Lenhard M, Tereza L, Heublein S, Ditsch N, Himsl I, Mayr D, Friese K, Jeschke U. Steroid hormone receptor expression in ovarian cancer: progesterone receptor B as prognostic marker for patient survival. BMC Cancer. 2012;12:553. Epub 2012/11/28. doi: 10.1186/1471-2407-12-553. PubMed PMID: 23176303; PMCID: PMC3575289.
24. Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Penault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L, Winer E. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017;28(12):3111. Epub 2017/03/23. doi: 10.1093/annonc/mdx036. PubMed PMID: 28327998; PMCID: PMC5834023.
25. Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, Johnston SR, Korde LA, Khatcheressian JL, Mehta RS, Muss HB, Burstein HJ. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016;34(25):3069-103. Epub 2016/05/25. doi: 10.1200/JCO.2016.67.1487. PubMed PMID: 27217461.
26. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast OaEC. https://www.nccn.org/professionals/physician_gls/default.aspx#site. Accessed July 15, 2020.2020.
27. Garcia-Becerra R, Santos N, Diaz L, Camacho J. Mechanisms of resistance to endocrine therapy in breast cancer: focus on signaling pathways, miRNAs and genetically based resistance. Int J Mol Sci. 2012;14(1):108-45. Epub 2013/01/25. doi: 10.3390/ijms14010108. PubMed PMID: 23344024; PMCID: PMC3565254.
28. Polivka J, Jr., Janku F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. Pharmacol Ther. 2014;142(2):164-75. Epub 2013/12/18. doi: 10.1016/j.pharmthera.2013.12.004. PubMed PMID: 24333502.
29. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009;9(8):550-62. Epub 2009/07/25. doi: 10.1038/nrc2664. PubMed PMID: 19629070.
30. Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009;8(8):627-44. Epub 2009/08/01. doi: 10.1038/nrd2926. PubMed PMID: 19644473; PMCID: PMC3142564.
31. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov. 2014;13(2):140-56. Epub 2014/02/01. doi: 10.1038/nrd4204. PubMed PMID: 24481312; PMCID: PMC3994981.

32. Janku F. Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: From laboratory to patients. Cancer Treat Rev. 2017;59:93-101. Epub 2017/08/06. doi: 10.1016/j.ctrv.2017.07.005. PubMed PMID: 28779636.
33. Yap TA, Bjerke L, Clarke PA, Workman P. Drugging PI3K in cancer: refining targets and therapeutic strategies. Curr Opin Pharmacol. 2015;23:98-107. Epub 2015/06/29. doi: 10.1016/j.coph.2015.05.016. PubMed PMID: 26117819; PMCID: PMC4728196.
34. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15(1):7-24. Epub 2014/12/24. doi: 10.1038/nrc3860. PubMed PMID: 25533673; PMCID: PMC4384662.
35. Janku F, Tsimberidou AM, Garrido-Laguna I, Wang X, Luthra R, Hong DS, Naing A, Falchook GS, Moroney JW, Piha-Paul SA, Wheler JJ, Moulder SL, Fu S, Kurzrock R. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther. 2011;10(3):558-65. Epub 2011/01/11. doi: 10.1158/1535-7163.MCT-10-0994. PubMed PMID: 21216929; PMCID: PMC3072168.
36. Hyman DM, Smyth LM, Donoghue MTA, Westin SN, Bedard PL, Dean EJ, Bando H, El-Khoueiry AB, Perez-Fidalgo JA, Mita A, Schellens JHM, Chang MT, Reichel JB, Bouvier N, Selcuklu SD, Soumerai TE, Torrisi J, Erinjeri JP, Ambrose H, Barrett JC, Dougherty B, Foxley A, Lindemann JPO, McEwen R, Pass M, Schiavon G, Berger MF, Chandarlapaty S, Solit DB, Banerji U, Baselga J, Taylor BS. AKT Inhibition in Solid Tumors With AKT1 Mutations. J Clin Oncol. 2017;35(20):2251-9. Epub 2017/05/11. doi: 10.1200/JCO.2017.73.0143. PubMed PMID: 28489509; PMCID: PMC5501365.
37. Iyer G, Hanrahan AJ, Milowsky MI, Al-Ahmadie H, Scott SN, Janakiraman M, Pirun M, Sander C, Socci ND, Ostrovnaya I, Viale A, Heguy A, Peng L, Chan TA, Bochner B, Bajorin DF, Berger MF, Taylor BS, Solit DB. Genome sequencing identifies a basis for everolimus sensitivity. Science. 2012;338(6104):221. Epub 2012/08/28. doi: 10.1126/science.1226344. PubMed PMID: 22923433; PMCID: PMC3633467.
38. Kwiatkowski DJ, Choueiri TK, Fay AP, Rini BI, Thorner AR, de Velasco G, Tyburczy ME, Hamieh L, Albiges L, Agarwal N, Ho TH, Song J, Pignon JC, Barrios PM, Michaelson MD, Van Allen E, Krajewski KM, Porta C, Pal S, Bellmunt J, McDermott DF, Heng DYC, Gray KP, Signoretti S. Mutations in TSC1, TSC2, and MTOR Are Associated with Response to Rapalogs in Patients with Metastatic Renal Cell Carcinoma. Clin Cancer Res. 2016;22(10):2445-52. Epub 2016/02/03. doi: 10.1158/1078-0432.CCR-15-2631. PubMed PMID: 26831717; PMCID: PMC4976069.
39. Wagle N, Grabiner BC, Van Allen EM, Amin-Mansour A, Taylor-Weiner A, Rosenberg M, Gray N, Barletta JA, Guo Y, Swanson SJ, Ruan DT, Hanna GJ, Haddad RI, Getz G, Kwiatkowski DJ, Carter SL, Sabatini DM, Janne PA, Garraway LA, Lorch JH. Response and acquired resistance to everolimus in anaplastic thyroid cancer. N Engl J Med. 2014;371(15):1426-33. Epub 2014/10/09. doi: 10.1056/NEJMoa1403352. PubMed PMID: 25295501; PMCID: PMC4564868.
40. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T, Franz DN. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363(19):1801-11. Epub 2010/11/05. doi: 10.1056/NEJMoa1001671. PubMed PMID: 21047224.
41. Cheng H, Zou Y, Ross JS, Wang K, Liu X, Halmos B, Ali SM, Liu H, Verma A, Montagna C, Chachoua A, Goel S, Schwartz EL, Zhu C, Shan J, Yu Y, Gritsman K, Yelensky R, Lipson D, Otto G, Hawryluk M, Stephens PJ, Miller VA, Piperdi B, Perez-Soler R. RICTOR Amplification Defines a Novel Subset of Patients with Lung Cancer Who May Benefit from Treatment with mTORC1/2 Inhibitors. Cancer Discov. 2015;5(12):1262-70. Epub 2015/09/16. doi: 10.1158/2159-8290.CD-14-0971. PubMed PMID: 26370156; PMCID: PMC4670806.
42. Grabiner BC, Nardi V, Birsoy K, Possemato R, Shen K, Sinha S, Jordan A, Beck AH, Sabatini DM. A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin

sensitivity. Cancer Discov. 2014;4(5):554-63. Epub 2014/03/19. doi: 10.1158/2159-8290.CD-13-0929. PubMed PMID: 24631838; PMCID: PMC4012430.
43. Moulder S, Helgason T, Janku F, Wheler J, Moroney J, Booser D, Albarracin C, Morrow PK, Atkins J, Koenig K, Gilcrease M, Kurzrock R. Inhibition of the phosphoinositide 3-kinase pathway for the treatment of patients with metastatic metaplastic breast cancer. Ann Oncol. 2015;26(7):1346-52. Epub 2015/04/17. doi: 10.1093/annonc/mdv163. PubMed PMID: 25878190; PMCID: PMC6267938.
44. Moulder S, Moroney J, Helgason T, Wheler J, Booser D, Albarracin C, Morrow PK, Koenig K, Kurzrock R. Responses to liposomal Doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer. J Clin Oncol. 2011;29(19):e572-5. Epub 2011/04/13. doi: 10.1200/JCO.2010.34.0604. PubMed PMID: 21482991.
45. Zhang S, Yu D. PI(3)king apart PTEN's role in cancer. Clin Cancer Res. 2010;16(17):4325-30. Epub 2010/07/14. doi: 10.1158/1078-0432.CCR-09-2990. PubMed PMID: 20622047.
46. Carnero A, Blanco-Aparicio C, Renner O, Link W, Leal JF. The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. Curr Cancer Drug Targets. 2008;8(3):187-98. Epub 2008/05/14. doi: 10.2174/156800908784293659. PubMed PMID: 18473732.
47. Wee S, Wiederschain D, Maira SM, Loo A, Miller C, deBeaumont R, Stegmeier F, Yao YM, Lengauer C. PTEN-deficient cancers depend on PIK3CB. Proc Natl Acad Sci U S A. 2008;105(35):13057-62. Epub 2008/08/30. doi: 10.1073/pnas.0802655105. PubMed PMID: 18755892; PMCID: PMC2529105.
48. Miller TW, Balko JM, Arteaga CL. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol. 2011;29(33):4452-61. Epub 2011/10/20. doi: 10.1200/JCO.2010.34.4879. PubMed PMID: 22010023; PMCID: PMC3221526.
49. Bosch A, Li Z, Bergamaschi A, Ellis H, Toska E, Prat A, Tao JJ, Spratt DE, Viola-Villegas NT, Castel P, Minuesa G, Morse N, Rodon J, Ibrahim Y, Cortes J, Perez-Garcia J, Galvan P, Grueso J, Guzman M, Katzenellenbogen JA, Kharas M, Lewis JS, Dickler M, Serra V, Rosen N, Chandarlapaty S, Scaltriti M, Baselga J. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. Sci Transl Med. 2015;7(283):283ra51. Epub 2015/04/17. doi: 10.1126/scitranslmed.aaa4442. PubMed PMID: 25877889; PMCID: PMC4433148.
50. Depowski PL, Rosenthal SI, Ross JS. Loss of expression of the PTEN gene protein product is associated with poor outcome in breast cancer. Mod Pathol. 2001;14(7):672-6. Epub 2001/07/17. doi: 10.1038/modpathol.3880371. PubMed PMID: 11454999.
51. Li S, Shen Y, Wang M, Yang J, Lv M, Li P, Chen Z, Yang J. Loss of PTEN expression in breast cancer: association with clinicopathological characteristics and prognosis. Oncotarget. 2017;8(19):32043-54. Epub 2017/04/15. doi: 10.18632/oncotarget.16761. PubMed PMID: 28410191; PMCID: PMC5458267.
52. Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res. 2012;18(21):5856-64. Epub 2012/10/20. doi: 10.1158/1078-0432.CCR-12-0662. PubMed PMID: 23082003.
53. Cancer) CCoSMi. Retrieved July 15, 2020, from http://cancer.sanger.ac.uk/cancergenome/projects/cosmic2020.
54. Genomics cfC. Retrieved July 15, 2020, from http://www.cbioportal.org/public-portal/2020.
55. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ, Global AT. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271-81. Epub 2007/06/01. doi: 10.1056/NEJMoa066838. PubMed PMID: 17538086.
56. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A, Group R-S. Efficacy of

everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449-56. Epub 2008/07/26. doi: 10.1016/S0140-6736(08)61039-9. PubMed PMID: 18653228.
57. Baselga J, Campone M, Piccart M, Burris HA, 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520-9. Epub 2011/12/14. doi: 10.1056/NEJMoa1109653. PubMed PMID: 22149876; PMCID: PMC5705195.
58. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Flinn I, Ghia P, Eradat H, Ervin T, Lamanna N, Coiffier B, Pettitt AR, Ma S, Stilgenbauer S, Cramer P, Aiello M, Johnson DM, Miller LL, Li D, Jahn TM, Dansey RD, Hallek M, O'Brien SM. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997-1007. Epub 2014/01/24. doi: 10.1056/NEJMoa1315226. PubMed PMID: 24450857; PMCID: PMC4161365.
59. Chen G, Chakravarti N, Aardalen K, Lazar AJ, Tetzlaff MT, Wubbenhorst B, Kim SB, Kopetz S, Ledoux AA, Gopal YN, Pereira CG, Deng W, Lee JS, Nathanson KL, Aldape KD, Prieto VG, Stuart D, Davies MA. Molecular profiling of patient-matched brain and extracranial melanoma metastases implicates the PI3K pathway as a therapeutic target. Clin Cancer Res. 2014;20(21):5537-46. Epub 2014/05/08. doi: 10.1158/1078-0432.CCR-13-3003. PubMed PMID: 24803579; PMCID: PMC4216765.
60. Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307(5712):1098-101. Epub 2005/02/19. doi: 10.1126/science.1106148. PubMed PMID: 15718470.
61. Sabatini DM. mTOR and cancer: insights into a complex relationship. Nat Rev Cancer. 2006;6(9):729-34. Epub 2006/08/18. doi: 10.1038/nrc1974. PubMed PMID: 16915295.
62. Hsu PP, Kang SA, Rameseder J, Zhang Y, Ottina KA, Lim D, Peterson TR, Choi Y, Gray NS, Yaffe MB, Marto JA, Sabatini DM. The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science. 2011;332(6035):1317-22. Epub 2011/06/11. doi: 10.1126/science.1199498. PubMed PMID: 21659604; PMCID: PMC3177140.
63. Yu Y, Yoon SO, Poulogiannis G, Yang Q, Ma XM, Villen J, Kubica N, Hoffman GR, Cantley LC, Gygi SP, Blenis J. Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. Science. 2011;332(6035):1322-6. Epub 2011/06/11. doi: 10.1126/science.1199484. PubMed PMID: 21659605; PMCID: PMC3195509.
64. Baselga J, Im SA, Iwata H, Cortes J, De Laurentiis M, Jiang Z, Arteaga CL, Jonat W, Clemons M, Ito Y, Awada A, Chia S, Jagiello-Gruszfeld A, Pistilli B, Tseng LM, Hurvitz S, Masuda N, Takahashi M, Vuylsteke P, Hachemi S, Dharan B, Di Tomaso E, Urban P, Massacesi C, Campone M. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(7):904-16. Epub 2017/06/04. doi: 10.1016/S1470-2045(17)30376-5. PubMed PMID: 28576675; PMCID: PMC5549667.
65. Di Leo A, Johnston S, Lee KS, Ciruelos E, Lonning PE, Janni W, O'Regan R, Mouret-Reynier MA, Kalev D, Egle D, Csoszi T, Bordonaro R, Decker T, Tjan-Heijnen VCG, Blau S, Schirone A, Weber D, El-Hashimy M, Dharan B, Sellami D, Bachelot T. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018;19(1):87-100. Epub 2017/12/11. doi: 10.1016/S1470-2045(17)30688-5. PubMed PMID: 29223745.
66. 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. Mol Cancer Ther. 2013;12(11):2319-30. Epub 2013/10/31. doi: 10.1158/1535-7163.MCT-12-0993-T. PubMed PMID: 24170767.
67. Westin JR. Status of PI3K/Akt/mTOR pathway inhibitors in lymphoma. Clin Lymphoma Myeloma Leuk. 2014;14(5):335-42. Epub 2014/03/22. doi: 10.1016/j.clml.2014.01.007. PubMed PMID: 24650973; PMCID: PMC4125533.
68. Yang Q, Modi P, Newcomb T, Queva C, Gandhi V. Idelalisib: First-in-Class PI3K Delta Inhibitor for the Treatment of Chronic Lymphocytic Leukemia, Small Lymphocytic Leukemia, and Follicular Lymphoma. Clin Cancer Res. 2015;21(7):1537-42. Epub 2015/02/12. doi: 10.1158/1078-0432.CCR-14-2034. PubMed PMID: 25670221; PMCID: PMC4523214.
69. Okkenhaug K, Burger JA. PI3K Signaling in Normal B Cells and Chronic Lymphocytic Leukemia (CLL). Curr Top Microbiol Immunol. 2016;393:123-42. Epub 2015/09/10. doi: 10.1007/82_2015_484. PubMed PMID: 26350103; PMCID: PMC4704136.
70. Ali K, Soond DR, Pineiro R, Hagemann T, Pearce W, Lim EL, Bouabe H, Scudamore CL, Hancox T, Maecker H, Friedman L, Turner M, Okkenhaug K, Vanhaesebroeck B. Inactivation of PI(3)K p110delta breaks regulatory T-cell-mediated immune tolerance to cancer. Nature. 2014;510(7505):407-11. Epub 2014/06/12. doi: 10.1038/nature13444. PubMed PMID: 24919154; PMCID: PMC4501086.
71. 13 CIsBV. 2021.
72. Elster N, Cremona M, Morgan C, Toomey S, Carr A, O'Grady A, Hennessy BT, Eustace AJ. A preclinical evaluation of the PI3K alpha/delta dominant inhibitor BAY 80-6946 in HER2-positive breast cancer models with acquired resistance to the HER2-targeted therapies trastuzumab and lapatinib. Breast Cancer Res Treat. 2015;149(2):373-83. Epub 2014/12/22. doi: 10.1007/s10549-014-3239-5. PubMed PMID: 25528022.
73. Paul J, Soujon M, Wengner AM, Zitzmann-Kolbe S, Sturz A, Haike K, Keng Magdalene KH, Tan SH, Lange M, Tan SY, Mumberg D, Lim ST, Ziegelbauer K, Liu N. Simultaneous Inhibition of PI3Kdelta and PI3Kalpha Induces ABC-DLBCL Regression by Blocking BCR-Dependent and -Independent Activation of NF-kappaB and AKT. Cancer Cell. 2017;31(1):64-78. Epub 2017/01/11. doi: 10.1016/j.ccell.2016.12.003. PubMed PMID: 28073005.
74. Schneider P, Schon M, Pletz N, Seitz CS, Liu N, Ziegelbauer K, Zachmann K, Emmert S, Schon MP. The novel PI3 kinase inhibitor, BAY 80-6946, impairs melanoma growth in vivo and in vitro. Exp Dermatol. 2014;23(8):579-84. Epub 2014/06/20. doi: 10.1111/exd.12470. PubMed PMID: 24942196.
75. Millis SZ, Ikeda S, Reddy S, Gatalica Z, Kurzrock R. Landscape of Phosphatidylinositol-3-Kinase Pathway Alterations Across 19784 Diverse Solid Tumors. JAMA Oncol. 2016;2(12):1565-73. Epub 2016/07/09. doi: 10.1001/jamaoncol.2016.0891. PubMed PMID: 27388585.
76. Haddadi N, Lin Y, Travis G, Simpson AM, Nassif NT, McGowan EM. PTEN/PTENP1: 'Regulating the regulator of RTK-dependent PI3K/Akt signalling', new targets for cancer therapy. Mol Cancer. 2018;17(1):37. Epub 2018/02/20. doi: 10.1186/s12943-018-0803-3. PubMed PMID: 29455665; PMCID: PMC5817727.
77. Owusu-Brackett N, Zhao M, Akcakanat A, Evans KW, Yuca E, Dumbrava EI, Janku F, Meric-Bernstam F. Targeting PI3Kbeta alone and in combination with chemotherapy or immunotherapy in tumors with PTEN loss. Oncotarget. 2020;11(11):969-81. Epub 2020/03/28. doi: 10.18632/oncotarget.27503. PubMed PMID: 32215185; PMCID: PMC7082117.

APPENDIX A: SCHEDULE OF ASSESSMENTS

Study Period	**Screening/ Baseline**	**Treatment**										**(EOT)/ Progression[a]**	**Post-Treatment**		
Treatment Cycle/ Title		**Cycle 1 (28 days)**				**Cycle 2 (28 days)**			**Subsequent cycles (28 days)**				**Safety follow-up visit[b]**	**Follow-up Visits**	**Survival Follow-up**
Day of cycle		1[c]	8	15	22	1	8	15	1	8	15	≤28 days from the last dose	30 days post last dose	Every 8 weeks	Every 12 weeks
Scheduling window	Days -28 to -1	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days	±7 days	±14 days
Informed consent	X														
PI3K pathway and PTEN status	X														
Hormone receptor expression status	X														
CMV, HBV and HCV testing[d]	X														
Demographics and Medical History	X														
Adverse event assessment[e]	X	CONTINUOUS													
Inclusion/exclusion criteria	X														
Cancer treatment history	X														
Prior/concomitant medications[f]	X	CONTINUOUS													
Archival tumor collection[g]	X														
Imaging and other															
CT/MRI	X								X[h]			X[h]		X[i]	

Study Period	**Screening/ Baseline**	**Treatment**										**(EOT)/ Progression[a]**	**Post-Treatment**		
Treatment Cycle/ Title		**Cycle 1**				**Cycle 2**			**Subsequent cycles**				**Safety follow-up visit[b]**	**Follow-up Visits**	**Survival Follow-up**
Day of cycle		1[c]	8	15	22	1	8	15	1	8	15	≤28 days from the last dose	30 days post last dose	Every 8 weeks	Every 12 weeks
Scheduling window	Days -28 to -1	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days	±7 days	±14 days
Tumor assessment	X								X[h]			X[h]		X[i]	
Study drug administration															
Copanlisib administration[j]		X	X	X		X	X	X	X	X	X				
Fulvestrant administration[k]		X		X		X			X						
Clinical Procedures															
Physical examination[l]	X	X	X	X	X	X		X	X			X			
ECOG performance status[l]	X	X	X	X	X	X		X	X			X			
Vital signs (BP[m], HR, body temperature, RR, O2 saturation)[l]	X	X	X	X	X	X		X	X			X			
Height	X														
Weight	X	X	X	X	X	X		X	X			X			
MUGA scan/ ECHO[n]	X														
Single 12 lead ECG	X	X				X			X						
Clinical laboratory tests															
Hematology (CBC plus differential)[o]	X	X	X	X	X	X		X	X			X			
Clinical chemistry[p]	X	X	X	X	X	X		X	X			X			
Urinalysis	X	X				X			X			X			

Study Period	Screening/ Baseline	Treatment										(EOT)/ Progression[a]	Post-Treatment		
Treatment Cycle/ Title		Cycle 1				Cycle 2			Subsequent cycles				Safety follow-up visit[b]	Follow-up Visits	Survival Follow-up
Day of cycle		1[c]	8	15	22	1	8	15	1	8	15	≤28 days from the last dose	30 days post last dose	Every 8 weeks	Every 12 weeks
Scheduling window	Days -28 to -1	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days	±7 days	±14 days
Blood collection for ctDNA[q]	X					X			X[q]			X			
Tumor biopsies[r]	X					X						X			
Pregnancy test	X[s]	X[t,u]				X[t]			X[t]						
FPG[v]	X	X	X	X		X	X	X	X	X	X				
Survival Status[w]															X

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CBC = complete blood count; CMV = cytomegalovirus; ctDNA = circulating tumor DNA; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FPG = fasting plasma glucose; h = hour(s); HBV = hepatitis B virus; HbsAg = HBV surface antigen; HbcAb = HBV core antibody; HCV = hepatitis C virus; HR = heart rate; IM = intramuscular; IV = intravenous; min = minute(s); MRI = magnetic resonance imaging; MUGA = multigated acquisition; O2 = oxygen; PCR = polymerase chain reaction; RR = respiratory rate; TB = Total bilirubin; WBC = white blood cell.

a) After discontinuation of study drugs, patients will complete an EOT visit within 28 days after the last study drug dose.
b) A safety follow-up visit is to be conducted 30 days (±7 days) after the last dose of study drug and later if drug-related AEs have not resolved at that time. After that, patients without documented disease progression will be followed every 8 weeks for disease assessments until documentation of disease progression. After documentation of disease progression, patients will be followed every 12 weeks for survival status; such follow-up will likely be conducted by telephone.
c) If Cycle 1 Day 1 occurs <72 hours after Screening, physical examinations, and clinical laboratory tests do not need to be repeated.
d) Patients will be excluded if they are positive for CMV or active HBV or HCV infection requiring treatment. CMV will be tested by PCR at screening. Active HBV (chronic or acute) is defined as having a known positive HbsAg at the time of screening, Participants with past HBV infection or resolved infection (defined as the presence of HbcAb and absence of HbsAg) are eligible if HBV DNA is negative. Participants with positive HCV antibody are eligible only if PCR is negative for HCV RNA.
e) AEs will be captured from the time of informed consent signing through 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever comes first.

f) All concomitant medication received within 28 days prior to study drug initiation and 30 days after the last dose of study drug will be recorded, including all prescription, over-the-counter, IV medications and fluids, supportive care drugs and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be recorded.
g) Archival tissue will be collected if available.
h) Radiographic tumor assessments, using CT scanning or MRI, will be performed at Screening, Cycle 3 Day 1 (±7 days), Day 1 (±7 days) of every 2nd cycle after that, and at EOT.
i) Patients who discontinue study treatment for a reason other than disease progression will move into follow-up phase. Patients will be monitored for disease status by tumor imaging (CT scan or MRI, as appropriate) every 8 weeks (±7 days) until PD, death, initiation of new anticancer therapy, withdrawal of consent, or lost to follow-up.
j) Copanlisib (60 mg IV) will be administered on Day 1, Day 8, and Day 15 of 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study drug for any other reason.
k) Fulvestrant (500 mg IM) will be administered on Day 1 and Day 15 of Cycle 1 and only Day 1 of any subsequent 28-day cycle.
l) Physical examination, performance status, vital signs and weight at baseline, weekly (D1, D8, D15, D22) during Cycle 1, twice during cycle 2 (D1 and D15), and then at the start of every cycle thereafter (within 3 days prior to treatment), or more frequently if clinically indicated. Finally at EOT/Progression.
m) On copanlisib infusion days, blood pressure should be measured pre-dose, mid-infusion, end of infusion, and 1 and 2 hours after the end of infusion. Note: a window of ± 10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement
n) MUGA scan or ECHO will be performed at screening and as clinically indicated. The same method should be used throughout the study.
o) Hematology (CBC with platelet and differential WBC count) will be performed at baseline, weekly (D1, D8, D15, D22) during Cycle 1, twice during cycle 2 (D1 and D15), and then at the start of every cycle thereafter (within 3 days prior to treatment), or more frequently if clinically indicated. Finally at EOT/progression.
p) Clinical chemistry (total protein, albumin, indirect and TB, AST, ALT, ALP, electrolytes [sodium, potassium, calcium, and magnesium], serum phosphate, serum creatinine, creatinine clearance, uric acid, and bile salts) will be performed at baseline, weekly (D1, D8, D15, D22) during Cycle 1, twice during cycle 2 (D1 and D15), and then at the start of every cycle thereafter (within 3 days prior to treatment), or more frequently if clinically indicated. Finally at EOT/progression.
q) Mandatory blood samples to isolate plasma ctDNA will be collected at pre-treatment (Day -28 to Day 1 of Cycle 1), on-treatment (pre-dose on the same day as the on treatment biopsy on Cycle 2 Day 1, as well as during the first two restaging visits), and post-treatment at EoT. A maximum of 5 ctDNA samples will be collected per patient.
r) Tumor biopsies, if medically feasible, will be obtained at Screening (within 28 days of Cycle 1 Day 1),on-treatment after fulvestrant and copanlisib administration on Cycle 2 Day 1 and at EOT. Tumor biopsies will be optional but encouraged, especially in patients with a response or prolonged disease control. Tumor biopsies will be used to evaluate genomic biomarkers of response and intrinsic and adaptive resistance, and to evaluate pharmacodynamic markers of engagement.
s) Pregnancy tests will be only for women with childbearing potential. Only whole blood will be collected for the pregnancy test that will be performed in the Screening period (Day -28 to Day -1).
t) Additional pregnancy tests will be performed at Day 1 of each Cycle only for women with childbearing potential. Whole blood or urine can be collected for the test.
u) Pregnancy test for Cycle 1 Day 1 can be skipped if the test for the screening period is performed close to the 1st cycle.

v) FPG testing will be performed at Screening and before each copanlisib administration on Day 1, Day 8, and Day 15 of each Cycle from Cycle 1 to Cycle 4 inclusive. Starting with Cycle 5, FPG testing will only be performed on Day 1 of each cycle.
w) Patients who experience confirmed disease progression or initiate a new anticancer therapy will move into the survival follow-up phase. Patients will be contacted by telephone every 12 weeks (±14 days) for survival status until death, withdrawal of consent, or lost to follow-up.

APPENDIX B: RECIST V1.1

Measurability of Tumor

Tumor lesions/lymph nodes will be categorized as measurable or non-measurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical examination (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest x-ray.

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 thickness recommended to be ≤5 mm).

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques suchas CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If non-cystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other locoregional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesions

Target Lesions
When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, and should be able to be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the eCRF in millimeters (or decimal fractions of centimeters [cm]).

Non-Target Lesions
All other lesions (or sites of disease) are identified as non-target lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and are not recorded or followed.

Response Criteria

Evaluation of Target Lesions
Completed 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. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter 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 (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when

progression was suspected.

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

Not Evaluable (NE): When an incomplete radiographical assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Non-Target Lesions
Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions is also considered progression.

***NE*:** When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response
The best overall response (BOR) is the best response recorded from the start of the study treatment until the earliest of objective progression or initiation of new anticancer therapy, taking into account any requirement for confirmation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. The BOR will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the study.

Time Point Response
It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is conducted/made at all at a particular time point, the patient is NE at that time point.) **Table 21** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 21: Time Point Response: Patients with Target (± Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Confirmatory Measurement/Duration of Response

Confirmation
To be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks (±3 days) after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and non-target lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of non-target lesions is not required.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease
SD is measured from the start of the treatment until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

APPENDIX C: NCI CTCAE V5.0

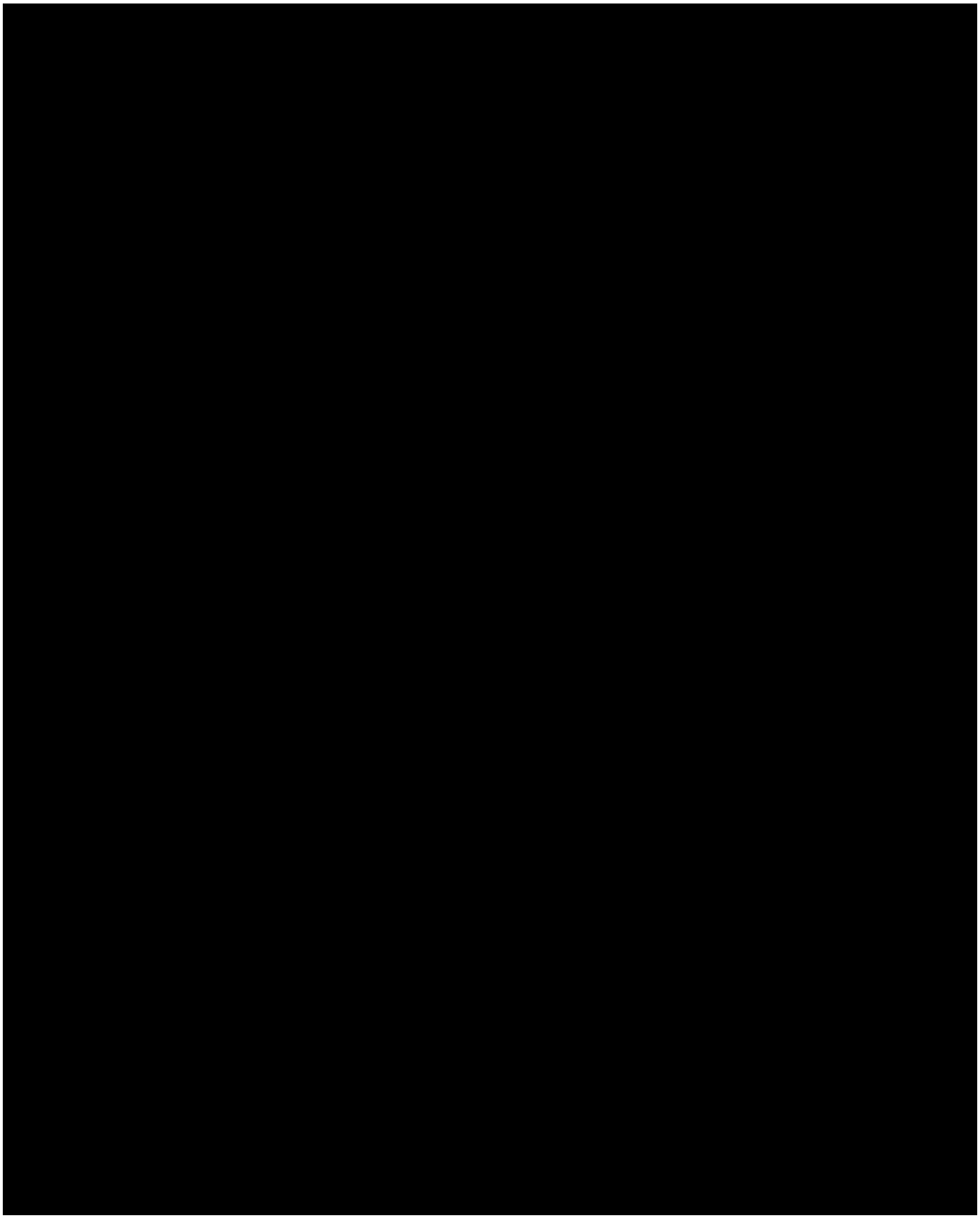
The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting.
(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

APPENDIX D: ECOG PERFORMANCE STATUS SCALE

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Oken MM, et al. Toxicity and response criteria of the ECOG. Am J Clin Oncol 1982;5:649-55.	

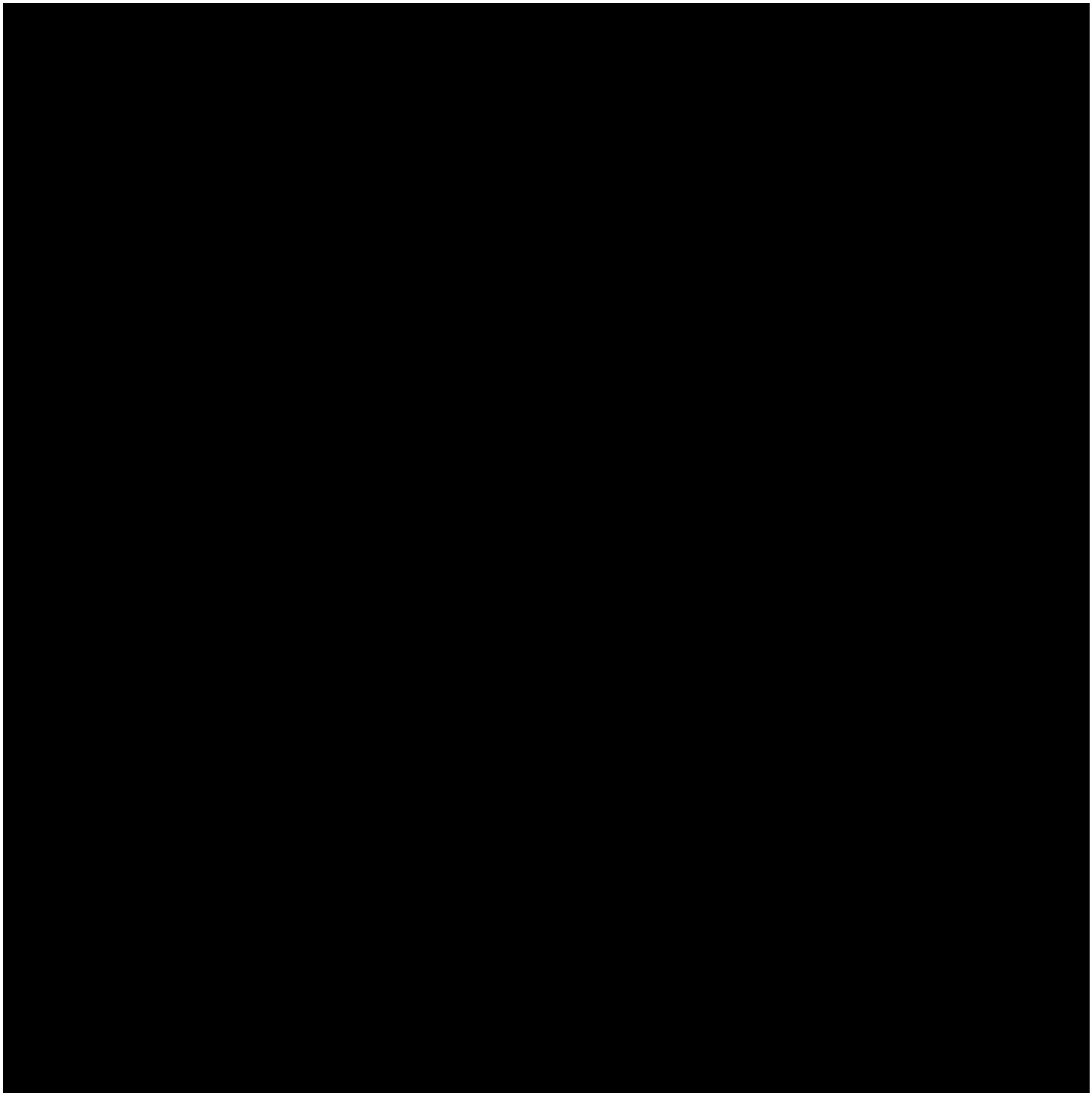
APPENDIX E: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATIONS

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of angina syndrome may be present at rest. If any physical activity is undertaken, discomfort is increased.



[redacted]

[redacted]



[redacted]