STUDY TITLE: Phase 1b Trial to evaluate safety and anti-tumor activity of AKT Inhibitor, Ipatasertib, in combination with endocrine therapy with/without CDK 4/6 inhibitor for Patients with Metastatic Hormone Receptor Positive/HER2 negative metastatic breast cancer (TAKTIC)

Brief Title: Targeting AKT after cyclin-dependent Kinase Therapy (TAKTIC)

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BIRMINGHAM IBS SYMPTOM QUESTIONNAIRE

The following questions ask you about your abdominal and bowel symptoms. When we use the word abdomen we mean belly/tummy. Some of the questions ask about passing a stool. By this we mean going to the toilet for a reason other than to urinate (pass water). All of these questions refer to the last 4 weeks.

Please tick one box for each statement.

| 1. During the last 4 weeks, how often have you had discomfort or pain in your abdomen? |
| 2. How often have you been troubled with loose, mushy or watery bowel motions during the last 4 weeks? |
| 3. How often during the last 4 weeks have you been troubled with diarrhoea? |
| 4. During the last 4 weeks how often have you been troubled by hard bowel motions? |
| 5. During the last 4 weeks how often have you felt the need to strain to pass a motion (stool)? |
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| 10. How often during the last 4 weeks have you suffered from a feeling of urgency (feeling that you must immediately rush to the toilet to pass a stool)? |
| 11. How often have you passed mucus or slime in your stools over the last 4 weeks? |

Requests for permission to utilise the Birmingham IBS symptom questionnaire should be sent to one of the following:

Andrea Rowle, Lesley Roberts, Sue Wilson, Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

APPENDIX D        BIOASSAY TEMPLATES
1. STUDY DESIGN AND OBJECTIVES

1.1 Study Design

This is an open-label study with three arms - Arm A) Doublet therapy: Fulvestrant with AKT inhibitor, ipatasertib, Arm B) Doublet therapy: Aromatase inhibitor (letrozole or anastrozole or exemestane, as per investigator discretion) with ipatasertib, and Arm C) Triplet Therapy: Fulvestrant with ipatasertib and palbociclib.

1.2 Primary Objectives

The primary objective of this trial is to evaluate the safety and tolerability of ipatasertib in combination with endocrine therapy (aromatase inhibitor or fulvestrant) with/without CDK 4/6 inhibitor (palbociclib), in patients with HR+/HER2- metastatic breast cancer who have received prior CDK 4/6 inhibitor.

1.3 Secondary and Exploratory Objectives

Secondary objectives include clinical efficacy (objective response rate, clinical benefit rate, progression-free survival, and overall survival). In addition, evaluation of fecal leukocytes and calprotectin level will be performed to evaluate for intestinal inflammation in patients who experience diarrhea during study treatment. Exploratory objectives include the identification of protein- and genomic-based predictors of response and resistance via a combination of immunohistochemical analysis of solid tumor specimens as well as next-generation sequencing efforts applied to both solid tumor specimens and circulating cell-free tumor DNA.
1.4 Hypothesis

Progression on CDK4/6-based therapy in HR+/HER2- metastatic breast cancer may define a population of patients with unique sensitivity to AKT-directed therapy and inhibition of AKT will be well tolerated in combination with anti-estrogen and CDK4/6-based therapy.

2. BACKGROUND

2.1 Endocrine Therapy for Hormone Receptor Positive (HR+) Breast Cancer

Endocrine therapy is the mainstay of management of HR+ breast cancer. Tamoxifen works by blocking the estrogen receptor in the breast cancer cells, acting as an antagonist and preventing estrogen from binding. While tamoxifen is approved for the treatment of metastatic breast cancer, approximately 30% of women will have primary resistance to the endocrine therapy; commonly defined as an incidence of recurrence within two years or progressive disease within six months while on adjuvant hormone therapy (Blanchette PS, 2013). Aromatase inhibitors function by blocking the enzyme aromatase, responsible for the conversion of peripheral androgens to estrogen in non-ovarian tissues; this constitutes the primary source of estrogen in post-menopausal women. There are two types of AIs: non-steroidal aromatase inhibitors (such as anastrozole and letrozole) and steroidal aromatase inhibitors (such as exemestane). Aromatase inhibitors, such as exemestane, are considered the preferred therapy option for postmenopausal HR+ breast cancer.

Unfortunately, despite optimal endocrine therapy, many patients with HR+ breast cancer have disease recurrence, likely related to the development of primary and secondary resistance to anti-
Estrogen therapy. Estrogen receptor (ER) activity is modulated by a variety of pathways in cancer cells whose modulation may mediate the emergence of clinical resistance.

2.2 AKT Inhibition as a Therapeutic Strategy

The PI3K/mTOR/AKT pathway is a well-described cellular signaling module with a multitude of roles in modulating cell growth, division, survival, and invasion/metastasis in many cancer types. Disruption of the PI3K/AKT/mTOR pathway has been implicated in resistance to endocrine therapy and disease progression. Activation of the PI3K/mTOR pathway by growth-factor receptors could result in estrogen-receptor independent signaling and cellular proliferation (Araki K, 2018). Furthermore, tumors harboring mutations in the receptor tyrosine kinases, such as PI3K and/or AKT, down-regulate the production of ER, thus reducing the dependence of the cell’s survival on ER.

Upregulation of Akt signaling (whether intrinsic or induced following chemotherapy) represents a potentially important survival pathway in response to genotoxic/mitotic stress (Xu N et al. 2012). Activation of Akt signaling following chemotherapy (including taxanes) may promote cell survival and chemoresistance across several cancer models, including breast cancer (Clark AS et al. 2002). Conversely, inhibition of the PI3K/Akt pathway in diverse cancers leads to radiosensitization and/or chemosensitization (Brognard J et al. 2001; Solit D et al. 2003; Wallin JJ et al. 2010).

Given the central function of the PI3K/AKT pathway in tumor cell growth, survival, and metastasis, novel strategies to target this signaling axis have been developed in multiple tumor
types. We have previously demonstrated the efficacy of AKT inhibition in combination with endocrine therapy utilizing ex-vivo circulating tumor cell lines derived from patients with HR+ metastatic breast cancer, (Yu M, 2014). We will evaluate the pre-clinical findings further in this phase 1b clinical trial with endocrine therapy and AKT inhibitor, ipatasertib.

2.3 Background on Ipatasertib

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase Akt. Ipatasertib binds to the activated conformation of Akt and is ATP competitive. Ipatasertib binding inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G₁ arrest and/or apoptosis in human cancer cells (Lin et al. 2012). In clinical tumor samples, robust Akt pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan et al. 2013).

In nonclinical models with high levels of phosphorylated Akt or PI3K/Akt pathway activity (i.e., \(PIK3CA\) mutation, \(PTEN\) alterations), sensitivity to ipatasertib has been observed across different tumor models, including breast cancers (Lin et al. 2013). Additionally, ipatasertib plus microtubule inhibitors or DNA-damaging chemotherapeutic agents showed a clear advantage over respective single-agent treatment in preclinical models (refer to the Ipatasertib Investigator’s Brochure for further information).

Based on the scientific rationale that PI3K/Akt blockade attenuates survival signals associated with mitotic stress from treatment with microtubule inhibitors and the high prevalence of
PI3K/Akt pathway activation signatures in TNBC and in HR+/HER2− tumors (Cancer Genome Atlas Network, 2012), clinical trials evaluating the preliminary safety and efficacy of the combination of ipatasertib and paclitaxel in patients with breast cancer have been conducted. These trials include a Phase Ib study with an expansion cohort of patients with HER2− breast cancer (Study PAM4983g, Arm C) and a randomized Phase II study (GO29227, LOTUS) comparing ipatasertib + paclitaxel versus placebo + paclitaxel as first-line treatment for patients with inoperable locally advanced or metastatic TNBC.

In the Phase Ib study PAM4983g, 3 of the 15 patients (20%) with breast cancer remained progression free for > 6 months (HR+/HER2−: n = 2; TNBC: n = 1), and 4 partial responses included patients who had prior exposure to paclitaxel or investigational PI3K inhibitors (HR+/HER2−: n = 2; TNBC: n = 2).

In the randomized Phase II study GO29227, one of the objectives was to investigate the added benefit of ipatasertib to paclitaxel in the subgroup of patients with PIK3CA/AKT1/PTEN-altered tumors. Results from this study showed improvement in median PFS in the intent-to-treat (ITT) population (hazard ratio = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm); and more pronouncedly in the pre-specified patient population with PIK3CA/AKT1/PTEN-altered tumors (hazard ratio = 0.44; 9 months vs. 4.9 months).

2.4 Emerging Mechanisms of Resistance to CDK4/6 Inhibitors Implicate AKT

The cyclin-dependent kinases 4 and 6 play a central role in the regulation of cellular division. In breast cancer cells estrogen-dependent signaling upregulates cyclin D1, which, in turn, binds
with and activates CDK4 and CDK6 (Sherr CJ, 2016). Activated CDK4/6 complexes phosphorylate and inactive the retinoblastoma (RB1) tumor suppressor, relieving inhibition of the E2F family of transcription which are required for upregulation of multiple targets instrumental in driving G1-to-S cell cycle progression. Novel therapeutic agents targeting CDK4/6 have been developed and, based upon a series of pivotal phase III studies, are FDA-approved in both the first- and subsequent-line setting for patients with metastatic HR+/HER2-breast cancer (Wander SA, 2017). Three agents are in widespread clinical use: palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio); these agents have very similar therapeutic efficacy with slight differences in dosing schedule and toxicity (Spring L, 2017). Aside from abemaciclib, they are approved for use only in combination with anti-estrogen agents – typically with an AI in the first-line setting and fulvestrant in AI-refractory patients.

Despite their widespread use, there is very little insight into the mechanisms governing response and resistance to these agents. Preclinical models have implicated RB1, cyclin E (CCNE), and CDK6 overexpression as potential modulators of resistance. Even less is known regarding potential clinical resistance mechanisms in breast cancer patients. Biallelic RB1 disruption has been described in a minority of individuals and may occur through a variety of molecular aberrations (Condorelli R, 2017; O'Leary B, 2018; Wander S, 2018). Alterations in PI3K have been identified in patients with advanced metastatic HR+ breast cancer, however these alterations do not themselves reliably predict resistance (O'Leary B, 2018).

Whole exome sequencing of well annotated biopsy specimens with exposure to CDK4/6-based therapy has suggested the landscape of resistance to these agents may be heterogeneous, with
multiple potential mediators implicated in subsets of patients (Wander S, 2018). Of note, in this cohort, diverse activated alterations in AKT1 have been identified, including point mutations and amplification events. Acquired AKT1 alterations were demonstrated via whole exome sequencing in two patients with matched pre/post exposure biopsy samples. Exogenous expression of AKT1 in HR+ breast cancer cell lines in vitro confers profound resistance to palbociclib, abemaciclib, and anti-estrogen therapy.

2.5 Rationale

Resistance to CDK4/6-based therapy is a significant problem in patients with metastatic HR+/HER2- breast cancer. These widely used agents often provoke durable responses, however clinical progression is unfortunately inevitable. New insights suggest that the genomic landscape of resistance to these agents is heterogeneous. Prior expectations that alterations in PIK3CA or RB1 would underlie the majority of clinical resistance have not been borne out in subsequent translational studies. Activating alterations in AKT1, however, have been identified in multiple patients, including in individuals with matched biopsy samples pre- and post- CDK4/6 exposure. Confirmatory molecular work in the laboratory suggests that activation of AKT1 may provoke significant resistance to both CDK4/6 inhibitors and standard anti-estrogens. Based upon the pre-clinical observations, a novel therapeutic strategy incorporating an AKT inhibitor and an anti-estrogen, with or without continuation of CDK4/6 inhibitor, warrants further evaluation in a clinical trial for patients with metastatic HR+/HER2- breast cancer.
3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

a. Adult women (≥ 18 years of age) with biopsy proven HR+/HER2 negative breast cancer; HR+ defined as ≥1% positivity for ER, and/or PR (≥1%), as per local assessment. HER2 as per standard CAP guidelines (local assessment).

b. Postmenopausal women with locally advanced or metastatic BC. Patients must be postmenopausal women as defined by one of the following:
   i. Women > 60 years OR
   ii. Women ≤ 60 years, and any one of following:
      - LH and FSH level in the postmenopausal range according to institutional standards
      - s/p post bilateral surgical oophorectomy
      - Premenopausal/perimenopausal women on gonadotropin-releasing hormone agonist (to be continued during study) and estradiol level in the postmenopausal range according to institutional standards

c. Disease progression on at least one prior therapy for metastatic disease, including endocrine therapy with/without CDK 4/6 inhibitor (palbociclib or ribociclib or abemaciclib). Disease recurrence during or within 12 months of completion/discontinuation of (neo)adjuvant endocrine therapy (with/without CDK 4/6 inhibitor) will count as one prior therapy for this definition. No upper limit on number of prior lines of endocrine therapy. 0-2 prior lines of chemotherapy for metastatic disease allowed. (Note: 0-2 prior line criteria refers to chemotherapy discontinued due to disease
progression. Chemotherapy discontinued before one cycle of treatment or due to adverse
effects would not count towards this definition for 0-2 prior line criteria).

d. ECOG Performance Status 0 – 2

e. Evaluable or measurable disease: at least one lesion that can be accurately measured in
at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with
spiral CT or MRI. Bone lesions in the absence of measurable disease as defined above is
also acceptable.

f. Discontinuation of prior breast cancer therapies

g. Prior mTOR inhibitor and/or PI3K inhibitor allowed (all arms)

h. Prior aromatase inhibitor is allowed (all arms)

i. Patients who have a history of a second malignancy are eligible, provided the
malignancy has been adequately treated, there is no ongoing treatment for the second
malignancy, and Overall PI approval is obtained.

j. Adequate bone marrow function: ANC ≥ 1000/mm3, hemoglobin ≥9 g/dl, and platelets
≥ 100,000/mm3.

k. Adequate hepatic function: Total bilirubin < 1.5mg/dL, AST and ALT < 3X Institutional
ULN (or 5 X Institutional ULN in presence of hepatic mets).

l. Adequate renal function: Calculated creatinine clearance ≥ 30 mL/min

m. Fasting blood glucose <140 mg/dL, and hemoglobin A1c <7.

n. Signed informed consent and agree to comply with study procedures.

o. Patient is a good candidate for the study, as per treating investigator.

p. Confirmation of adequate archival tissue (20 unstained slides cut at 5 μm or 1 block) or
pre-treatment biopsy required before study entry. If adequate tissue is not available, PI
approval is required prior to study entry.

3.2 Exclusion Criteria

a. Participants with progressive CNS metastatic disease. Patients with stable CNS metastasis would be eligible, provided mets radiologically decreasing/stable for at least one month, and patient is not actively taking steroids.

b. Participants who have had anti-cancer therapy, including endocrine therapy or targeted therapy or antibody-based therapy or immunotherapy or chemotherapy or radiotherapy, within 2 weeks prior to entering the study or those who have not recovered from clinically significant adverse events (grade 2 or higher). Asymptomatic lab abnormality (grade 2 or higher) could be allowed after discussion and approval by PI.

c. Prior use of AKT inhibitor (any setting).

d. Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as

http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians’ Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
e. Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., inflammatory bowel disease, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

f. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:

   i. History of angina pectoris, symptomatic pericarditis, coronary artery bypass graft (CABG) or myocardial infarction within 6 months prior to study entry.

   ii. Known (documented) cardiomyopathy, i.e. known left ventricular ejection fraction (LVEF) < 50% (ECHO or MUGA not needed specifically for this trial).

   iii. History of cardiac failure, significant/symptomatic bradycardia, Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome or any of the following:

      1. Known risk to prolong the QT interval or induce Torsade’s de Pointes.

      2. Uncorrected hypomagnesemia or hypokalemia of Grade 3 or higher.

      3. Systolic Blood Pressure (SBP) >160 mmHg or <90 mmHg.
4. Bradycardia (heart rate < 50 at rest), by ECG (based on a mean of 3 ECGs) or pulse.

5. On screening, QTcF > 470 screening ECG (based on a mean of 3 ECGs).

g. History of clinically significant, uncontrolled GI toxicity that lead to discontinuation of a previous oral cancer therapy regimen

h. Uncontrolled pleural effusion, pericardial effusion, or ascites, as judged by the investigator

i. HIV-positive participants on combination antiretroviral therapy are ineligible. These participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

j. History of Type I or Type II diabetes mellitus requiring insulin. Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment. Patients must meet the laboratory eligibility criteria for fasting blood glucose and hemoglobin A1c as outlined in the inclusion criteria.

k. Pregnant women are excluded from this study because the safety of study medications is not established in pregnant women.

l. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. In the case of bilateral oophorectomy alone, only when the reproductive status of the
woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Highly effective contraception methods include:

a. Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

c. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

d. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Note: While oral contraceptives are allowed, they should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

m. For Arm C only: h/o of intolerable toxicity to CDK 4/6 inhibitor resulting in treatment discontinuation due to toxicity.
n. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

o. Patient has any condition that would preclude enrollment, as per investigator judgement.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant
does not receive protocol therapy following registration, the participant’s registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

One cycle will be considered a four-week period. Ipatasertib (oral) will be administered on days 1-28 of each cycle for arms A and B. In Arm C, Ipatasertib (oral) will be given on days 1-21 and palbociclib (oral) on days 8-28. However, additional schedules may be explored. The choice of Arm A, B, C would be as per treating investigator considering eligibility criteria and open slots/cohorts, after discussion with PI if needed. Antihistamine prophylaxis for rash could be added in the first two cycles as per discretion of treating investigator.

Aromatase inhibitors will be administered (oral) on days 1-28 of each cycle for arm B.

Fulvestrant (intramuscular) will be given as per standard of care, i.e. twice a month (day 1,15) for the first cycle, and then monthly.

**Arm A and B**

This is an open-label study. Patients in Arm A will receive Fulvestrant with ipatasertib (N = approximately 15), and Arm B will receive Aromatase inhibitor (letrozole or anastrozole or
exemestane, as per investigator discretion) with ipatasertib (N = approximately 15). Ipatasertib will be administered on days 1-28 of each cycle for arms A and B. Fulvestrant will be given as per standard of care. In patients who have never received Fulvestrant before (or have not received Fulvestrant in the past 3 months as of C1D1), it would be administered twice a month (day 1,15) for the first cycle, and then monthly. In patients (or have received Fulvestrant in the past 3 months as of C1D1), who are already on Fulvestrant before start of the trial, Fulvestrant would be continued monthly.

For arms A and B, we will start at recommended dose of ipatasertib (400 mg), along with a standard dose of fulvestrant (arm A), or aromatase inhibitor (arm B). If ipatasertib at 400 mg is considered too toxic (based on DLTs as outlined in the stats section), we will explore lower doses including 300 mg (dose level -1) and 200 mg (dose level -2), but will not explore doses lower than 200 mg of ipatasertib (dose level -2). However, additional schedules (such as intermittent schedule) could be explored based on safety and tolerability of the doublet combination, after discussion with study committee. The DLT criteria are listed at the end of section 5.1.

Based on its mechanism of action and preclinical toxicology studies, there should not be major potential overlapping toxicities between endocrine therapy and ipatasertib, and accordingly we will utilize standard dose for both to confirm safety and tolerability. The potential overlapping toxicity between palbociclib and ipatasertib includes diarrhea (will be monitored closely and managed with anti-diarrheal medications), and there is theoretical concern of drug-drug interaction. Primary prophylaxis with loperamide is mandated during first cycle and adjusted as
clinically indicated, as outlined in section 6.1. In addition, in patients who have diarrhea, we will conduct comprehensive evaluation including measurement of fecal leukocytes and calprotectin level to evaluate for intestinal inflammation. Finally, we will start with three weeks (days 1-21) of 28 day cycle schedule for ipatasertib. Patients will dose for the last 3 weeks (days 8-28) of 28 day cycle schedule for palbociclib.

**Arm C**

In Arm C, patients will receive fulvestrant and palbociclib with ipatasertib. There will be dose-escalation (N = approximately 15-30) followed by dose-expansion (N = approximately 15). Standard 3+3 design will be utilized for dose-escalation decisions.

The objective of dose escalation in arm C is to determine the maximum tolerated dose (MTD) of fulvestrant and palbociclib with ipatasertib that can be given safely in a single cycle. Patients will be monitored each week prior to the next course of treatment to ensure they do not have ≥ Grade 2 toxicities. The DLT criteria are listed at the end of section 5.1.

Starting with 3 patients at the lowest dose level (D0), 3 patients will be enrolled, treated, and monitored during the 28-day DLT evaluation period. Several increasing dose levels are then examined sequentially. If no patient experiences a DLT, then the testing moves on to the next higher dose level and the process is repeated. If one patient experiences a DLT, then up to 3 more patients are tested at the same dose level. Only 1 out of the 6 of these patients can experience a DLT for the testing to move on to the next higher dose level. At any dose level, if 2 patients tested experience a DLT, that dose level will be deemed to have unacceptable toxicity...
and will be abandoned from further study. In this event, testing of the dose level immediately below the poorly tolerated dose level will be expanded, if necessary, to include a total of 6 patients. If at most 1 patient experiences a DLT, this dose level is then considered the MTD. The process of escalation and de-escalation is repeated until the MTD is reached (highest dose level for which 6 patients were treated with at most 1 DLT occurrence). If 2 DLT’s occur at the first dose level, an additional 3-6 patient cohort will be treated at a de-escalated dose level (D0a*, see Section 6). If this is too toxic, the study will be halted until further discussions with the FDA regarding how to proceed. If the highest planned dose level has been tested and shown to have acceptable toxicity, no MTD can be declared. The DLT evaluation period will be days 1-28 of the first treatment cycle. The target enrollment cohort size is 3-6 patients per cohort. Additional patients could be enrolled in cohorts to replace unevaluable patients or obtain additional safety/biomarker data that would help with dose-escalation decision.

For arm C, we will start at recommended dose of fulvestrant (500 mg) and palbociclib (125 mg), along with ipatasertib, 3 week on and 1 week off schedule. We will start with 200 mg ipatasertib, 3 week on and 1 week off schedule (lowest dose; dose level 1), as outlined in Table 1. If considered safe, we will increase ipatasertib to 300 mg (dose level 2) and then 400 mg (dose level 3), as per 3+3 design. In dose-level 2, we will start with palbociclib at 125 mg (dose level 2a), and if dose-escalation criteria are met (as per 3+3 rule), will move to dose level 3a (ipatasertib at 400 mg and palbociclib at 125 mg), but if not met, will explore additional dose-levels with lower dose of palbociclib (dose levels 2b, and 2c if needed) and if considered safe, proceed with additional dose-escalation (dose levels 3b, and 3c if needed). If dose level 1 is considered too toxic, will explore lower dose of palbociclib (100 mg dose level -1; and 75 mg
dose level -2), but will not explore doses lower than 200 mg of ipatasertib and 75 mg of palbociclib (dose level -2). Both ipatasertib and palbociclib will be given for three weeks (days 1-21) of 28 day cycle. Ipatasertib (oral) will be given on days 1-21 and palbociclib (oral) on days 8-28, but additional schedules could be explored. One cycle will be considered a four-week period. Fulvestrant will be given at the recommended dose in all cohorts. In patients who have never received Fulvestrant before (or have not received Fulvestrant in the past 3 months as of C1D1), it would be administered on Days 1 & 15 for Cycle 1, and then on Day 1 of each subsequent cycle. In patients who have received Fulvestrant in the past 3 months as of C1D1 who are already on Fulvestrant before start of the trial, Fulvestrant will be administered on Day 1 of every cycle. Additional schedules will be explored based on safety and tolerability of the triplet combination. Additional patients may be enrolled to have adequate number of evaluable patients for safety and dose-escalation decisions. The study committee, including PI, will be involved in dose-escalation and decision to open new cohorts. A new dose-escalation cohort will only open after approval by IRB and communication to the research team.

Dose-holds (and modifications) due to DLT will be handled the same as the criteria for dose modification toxicity criteria. Criteria to treat (dose-holds and modifications) due to DLT will be handled the same as the criteria for dose modification due to toxicity and restart guidelines listed in section 6.

Table 1. Planned Dose Escalation Schema for Arm C*

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ipatasertib</th>
<th>Ipatasertib</th>
<th>Palbociclib</th>
<th>Palbociclib</th>
<th>Cohort Size</th>
</tr>
</thead>
</table>

24
<table>
<thead>
<tr>
<th></th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D-2</td>
<td>200</td>
<td>Days 1-21,</td>
<td>75</td>
<td>Days 8-28,</td>
<td>3-6 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 28 days*</td>
<td></td>
<td>every 28 days*</td>
<td></td>
</tr>
<tr>
<td>D-1</td>
<td>200</td>
<td></td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>200</td>
<td></td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2a</td>
<td>300</td>
<td></td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2b</td>
<td>300</td>
<td></td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2c</td>
<td>300</td>
<td></td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3a</td>
<td>400</td>
<td></td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3b</td>
<td>400</td>
<td></td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3c</td>
<td>400</td>
<td></td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ipatasertib (oral) will be given on days 1-21 and palbociclib (oral) on days 8-28, but additional schedules could be explored.

**DLT criteria**

Dose-limiting toxicity (DLT), for all the three arms (A,B,C) will be defined based on the first treatment cycle as any of the following events, possibly related to study drugs. In general, all AEs of the specified grades, as listed below, should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes:

- Any Grade 4 neutropenia ≥ 7 days,
- Neutropenic fever
- Grade 4 thrombocytopenia ≥ 7 days,
- Grade 3+ thrombocytopenia with bleeding
- Grade 4 anemia ≥ 5 days,
• Any ≥ Grade 3 nausea, vomiting, or diarrhea which persists for > 72 hours despite optimal medical management and other supportive care,

• For patients with hepatic metastases, AST or ALT > 8xULN or AST or ALT >5x ULN for >=14 days

• Hy's law

• Grade 3+ electrolyte abnormality that lasts >72 hours, unless the patient has clinical symptoms, in which case all grade 3+ electrolyte abnormality regardless of duration should count as a DLT. Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT.

• Grade 3+ fatigue >= 1 week

• Any death not clearly due to the underlying disease or extraneous causes

• Any other ≥ Grade 3 non-hematologic toxicity, despite maximal medical management and due to treatment, including Grade 3 infusion-related toxicity.

5.2 Pre-Treatment Criteria

Required within 4 weeks prior to treatment:

• Signed informed Consent

• Documented histology review to confirm metastatic breast cancer.

• Medical/surgical history review

• Concomitant medications review

• Standard triplicate 12-lead electrocardiogram (EKG)

• CBC including platelet count, with WBC differential in absolute cell counts
- Routine serum chemistries (*i.e.*, glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, NA, K, calcium, CL, CO\textsubscript{2}) and Hemoglobin A1C
- CT or MRI with contrast (chest, abdomen, pelvis, other regions of known/suspected involvement)
- Bone Scans (or PET/CT with bone window)
- Serum biomarkers as appropriate for disease
- Adverse event reporting

### 5.3 Agent Administration

Patients do not need to re-meet eligibility criteria on cycle 1 day 1. Treatment can be administered prior to the results of the tests that are general clinical labs but not required as specific criteria for treatment (section 6 Tables).

Ipatasertib is intended for oral administration and will be supplied as 100- and 200-mg tablets. For information on the formulation and handling of ipatasertib, see the Ipatasertib Investigator’s Brochure. The period between re-dispensing and last tablet consumed should not exceed 1 month. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsor.

A sufficient amount of ipatasertib should be provided to the patient to last for up to one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib
and their medication diaries to each study visit. Ipatasertib should be stored between 59°F to 86°F (15°C to 30°C) in the original container that includes the desiccant.

Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib may be taken with or without food. If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. Ipatasertib should be taken at approximately the same time each day, and it can be taken at night (with palbociclib in Arm C) per treating physician discretion.

On clinic days, including fulvestrant administration (arm A and C), patients will be instructed to take their morning oral dose of ipatasertib (and palbociclib for arm C, when applicable) in the clinic after completion of the pretreatment assessments, as outlined in Study calendar (section 10). The dose of ipatasertib will be taken at home, as directed on all nonclinic days. Ipatasertib (and palbociclib for arm C) should be taken at approximately the same time each day. On study days requiring a predose blood draw for PK sampling, patients will be instructed to take their daily oral dose of ipatasertib in the clinic after completion of the pretreatment assessments. Time of dose administration will be collected on the PK sampling day and for prior doses administered for up to 2 days before a PK sampling visit. Any incidence of vomiting within 3 hours post drug administration should also be recorded for the day of PK sampling.
5.4 General Concomitant Medication and Supportive Care Guidelines

- Concomitant treatment considered necessary for the patient’s well-being (i.e. antiemetics, analgesics, megestrol acetate for anorexia) may be given at discretion of the treating physician.

- Patients enrolled in this trial will likely be refractory or relapsed after one or more chemotherapy regimens and may have also received antibody therapy. All treatments must be discontinued for a minimum of 2 weeks before starting this trial. Other anti-cancer treatment is not permitted during this study. Palliative and/or supportive medications and procedures are permitted at the physician’s discretion.

- In the event of severe or prolonged hematological toxicity, hematopoietic growth factors or blood transfusions are permitted to prevent anticipated cytopenias. These are not permitted prophylactically.

- High dose corticosteroids are not allowed within 2 weeks of beginning this study. Low dose corticosteroids <10 mg prednisone or equivalent daily are allowed. Use of steroids for contrast prophylaxis is allowed and does not count towards the “high dose corticosteroids” criteria.

- Antiemetics, cytokines, or blood transfusions are not permitted prophylactically. However, they may be administered as clinically necessary in the event of severe or prolonged toxicity.

- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window (see Appendix) should be
avoided/used with caution during the study treatment period and for 28 days after the last dose of study treatment.

- Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study treatment period and for 28 days after the last dose of study treatment. Consumption of St. John’s wort, a potent CYP3A4 enzyme inducer, is prohibited during the study treatment period, and for 28 days after the last dose of study treatment.

- Concomitant medications and treatments, such as herbal supplements, palliative care, supportive care drugs (e.g. antiemetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, blood products, and nondrug interventions (e.g. paracentesis) are permitted at the physician’s discretion. The reporting of concomitant medications should end when a patient starts a new anti-cancer treatment and thus, unenrolls from the study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

- Antihistamine prophylaxis for rash could be added in the first two cycles as per discretion of treating investigator.

- CNS radiation may be permitted on the clinical trial, if new CNS metastases are discovered, or if progressive disease in the CNS occurs, in the absence of systemic progression, if it is amenable to radiation and/or surgery if treatment is indicated. The study treatment (ipatasertib +/- palbociclib) should be held for at least 7 days before, during, and at least 7 days after CNS radiation or surgery. Treatment with endocrine therapy can be continued through radiation/surgery, as
per discretion of treating investigator. If CNS disease is treated, in order to continue on study, the study treatment must be resumed within 42 days of the last dose. If study treatment is resumed, the date of first CNS disease progression will be considered for statistical analysis.

5.5 Criteria for Taking a Participant off Protocol Therapy

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

- Disease progression (Note, if a patient is deriving clinical benefit from treatment and treating physician wants to continue treatment, the patient may continue treatment after approval of PI. In terms of statistics and result reporting, the date of first disease progression will be considered for survival analysis).
- Inter-current illness that prevents any further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be
documented in the case report form (CRF) and OnCore. Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, at 617-726-5000.

5.6 Duration of Follow Up

After last dose of study treatment, all patients, including patients who prematurely terminated study participation, will be followed every 3 months for survival follow-up. Follow-ups may be in-clinic or made by telephone. Any further active anti-cancer treatment will be documented. For 30 days after the last dose of study treatment, adverse event reporting will continue. After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). The research team will update the relevant Off Treatment/Off Study information in OnCore.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.
6. DOSING DELAYS/DOSE MODIFICATIONS

Any dose interruption, dose modification, overdose or incorrect administration of ipatasertib should be noted on the corresponding study drug administration eCRF. The drug hold would not affect dosing or assessment schedule; i.e when a drug is held, particularly in the middle of a cycle, the cycle day count will stay the same (cycle will not restart). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5 can be downloaded from the CTEP website


6.1 Risks associated with Ipatasertib

Hyperglycemia, including cases of Grade 3 or Grade 4 hyperglycemia, has been reported in patients receiving ipatasertib as monotherapy or ipatasertib in combination with other anticancer drugs or hormonal therapy. Hyperglycemia of any grade, regardless of causality, was reported in 35.3% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, with Grade 3 hyperglycemia occurring in 1 patient (2.0%). In the GO27983 study, hyperglycemia of any grade, regardless of causality, was reported in 22.6%, 9.1%, and 7.4% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 hyperglycemia occurred in 10.7%, 2.3%, and 2.5% of patients in the 400 mg, 200 mg, and placebo arms, respectively. One patient (1.2%) in the ipatasertib 400 mg arm experienced Grade 4 hyperglycemia. There were no other instances of Grade 4 or higher hyperglycemia events in any arm. In the GO29227 study, hyperglycemia of any grade, regardless of causality, was
reported in 9.5% and 3.3% of patients in the ipatasertib 400 mg and placebo arms, respectively. There were no reports of Grade ≥3 hyperglycemia.

GI toxicities such as nausea, vomiting, diarrhea, and stomatitis/oral mucositis have been commonly observed in patients receiving ipatasertib as monotherapy or in combination with other anticancer drugs. GI toxicities of any grade, regardless of causality, were commonly reported in patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, including nausea (78.4%), diarrhea (72.5%), vomiting (58.8%), and stomatitis or mucosal inflammation (7.8%). In this study, the reported Grade 3 GI toxicities included diarrhea (7.8%), and nausea (2.0%). In the GO27983 study, GI toxicities, irrespective of grade or causality (presented by proportion of patients affected in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively), included diarrhea (77.4%, 48.9%, and 24.7%), nausea (53.6%, 35.2%, and 24.7%), vomiting (32.1%, 27.3%, and 14.8%), and oral mucositis (6.0%, 3.4%, and 1.2%). The only Grade 3 GI AEs that affected ≥2 patients, irrespective of causality, were diarrhea (13.1%, 2.3%, and 1.2%) and nausea (2.4%, 0%, and 0%). There were no Grade 4 or 5 events in this category in this study. In the GO29227 study, GI toxicities of any grade, regardless of causality, reported in the ipatasertib 400 mg and placebo arms, respectively, included diarrhea (92.1% and 20.0%), nausea (52.4% and 33.3%), vomiting (27.0% and 23.3%), and oral mucositis (23.8% and 15.0%). Grade 3 diarrhea occurred in 22.2% of the ipatasertib 400 mg arm and 0% of the placebo arm. Grade 3 vomiting was reported in 3.2% and 0% of the ipatasertib 400 mg and placebo arms, respectively. With regard to Grade 3 nausea and Grade 3 oral mucositis, there was 1 patient in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively).
There were no Grade 4 or Grade 5 diarrhea, nausea, vomiting, or oral mucositis events in any arm.

Rash, primarily manifested as maculo-papular type with or without pruritus, has been commonly reported in patients receiving treatment with ipatasertib. Rash-related events of any grade, regardless of causality, were reported in 15.7% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g; Grade 3 rash (toxic skin eruption as reported term) was reported in 1 patient (2.0%). In the GO27983 study, irrespective of grade or causality, the proportion of patients experiencing a rash-related event was 23.8%, 9.1%, and 6.2% in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively. Of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, 9.5%, 2.3%, and 0%, experienced Grade 3 rash, respectively. One patient (1.2%) in the ipatasertib 400 mg arm experienced a Grade 4 event. There were no other instances of Grade ≥4 events in this study. In the GO29227 study, rash of any grade, regardless of causality, was reported in 30.2% and 30.0% of the ipatasertib 400 mg and placebo arms, respectively. There was 1 patient with Grade 3 rash in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively). There were no cases of Grade 4 or Grade 5 rash events in any arm. Cases of Grade 3 rash requiring dose interruption and treatment with topical or systemic corticosteroids have also been observed from other ongoing ipatasertib studies. Given the experience from other prior studies, antihistamine prophylaxis for rash could be added in the first two cycles, as per discretion of treating investigator, in this study (TAKTIC).
Fatigue or asthenia of any grade, regardless of causality, has been observed in 62.7% of patients receiving ipatasertib as a single agent in the Phase I Study PAM4743g, with 5 (9.8%) cases of Grade 3 asthenia/fatigue reported. In the GO27983 study, asthenia/fatigue of any grade, irrespective of causality, was reported in 48.8%, 45.5%, and 43.2% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 asthenia/fatigue occurred in 9.5%, 5.7%, and 3.7% of patients, respectively, as above. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm. In the GO29227 study, asthenia/fatigue of any grade, regardless of causality, was reported in 49.2% and 43.3% of the ipatasertib 400 mg and placebo arms, respectively. Grade 3 asthenia/fatigue was reported in 6.3% and 6.7% of the ipatasertib 400 mg and placebo arms, respectively. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm.

Refer to the Ipatasertib Investigator’s Brochure for updated information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single agent and in combination with chemotherapy.

6.2 Management for Ipatasertib Toxicity (Arm A and B)

Dose modifications for ipatasertib therapy are provided below in Table 2. Patients may hold the ipatasertib for up to 28 consecutive days to recover from toxicity or an adverse event related to the study drug. There is no duration limit for holding endocrine therapy. If the ipatasertib is discontinued at any time during the study, patients may have the option of continuing standard endocrine therapy. Alternatively, if the standard endocrine therapy is discontinued at any time during the study based on investigator discretion, patients may have the option of continuing
ipatasertib. Please note the guidelines are suggested recommendations (not mandatory), and investigator should treat patient considering safety and tolerability.

The suggested treatment modifications related to Ipatasertib for gastrointestinal toxicity are outlined in Table 3.1, hematological toxicity in Table 3.2, hepatic toxicity in Table 3.3, hyperglycemia toxicity in Table 3.4, rash in Table 3.5, and other toxicities in Table 3.6.

Table 2. Dose modifications for ipatasertib therapy

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ipatasertib Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Dose</td>
<td>400</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>300</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>200*</td>
</tr>
</tbody>
</table>

* Dose reduction below 200 mg is not allowed. For patients requiring dose reduction below 200 mg, one option would be to consider intermittent schedule (such as days 8-21, every 28 days), after discussion with the principal investigator.

Dose modification for gastrointestinal adverse effects

Diarrhea is a common adverse event noted with ipatasertib. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle, and investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgment. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide includes use of loperamide 2 mg every 4 hours or after each
loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with water and electrolyte-containing liquids. Stool collection for patients experiencing diarrhea is outlined in the biomarker plan (section 9). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed.

Table 3.1 Suggested Treatment Modifications for Gastrointestinal Toxicity Possibly Related to Ipatasertib

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>Ipatasertib</th>
</tr>
</thead>
</table>
| **Prophylaxis** | • All patients should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle.  
  • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated. |
| **Grade 1** | • No requirement for dose interruption or dose reduction  
  • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval.  
  • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals.  
  • Collect stool specimen during diarrheal episode (details in biomarker section 9). Upon diarrhea resolution, loperamide prophylaxis can be considered and continues as clinically indicated. |
| **Grade 2** | • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated.  
  • Collect stool specimen during diarrheal episode (details in biomarker section 9). Rule out infectious etiology. Consider GI consult for diarrhea lasting more than 5 days.  
  • Reduce ipatasertib by one (or more) dose level for recurrent Grade 2 diarrhea.  
  • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. |
### Diarrhea

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle.</td>
<td>Dietary modifications, such as avoiding any lactose-containing foods and eating small meals.</td>
</tr>
<tr>
<td>After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated</td>
<td>Hydration</td>
</tr>
<tr>
<td>For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil, codeine, or octreotide, or as per institutional guidelines.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat per Grade 2 management guidelines and supportive care.</td>
<td>Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron and prochlorperazine. Consider Olanzapine for patients with delayed/refractory/anticipatory nausea.</td>
</tr>
<tr>
<td>Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted.</td>
<td>Hold ipatasertib</td>
</tr>
<tr>
<td>For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level.</td>
<td>Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron and prochlorperazine. Consider Olanzapine for patients with delayed/refractory/anticipatory nausea.</td>
</tr>
<tr>
<td>When study treatment is resumed, loperamide prophylaxis should also be considered and continued as clinically indicated.</td>
<td>Resume Ipatasertib reduced by 1 dose level if toxicity resolves to Grade ( \leq 1 ) or baseline within 4 weeks</td>
</tr>
<tr>
<td>Exception: Nausea lasting ( \leq 72 ) hours</td>
<td>Exception: Nausea lasting ( \leq 72 ) hours</td>
</tr>
<tr>
<td>If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
<td>If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
</tr>
<tr>
<td>Permanently discontinue if toxicity does not improve to Grade ( \leq 1 ) or baseline within 4 weeks.</td>
<td>Permanently discontinue if toxicity does not improve to Grade ( \leq 1 ) or baseline within 4 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently discontinue ipatasertib.</td>
<td>Permanently discontinue ipatasertib</td>
</tr>
<tr>
<td>Treat per Grade 2 management guidelines and supportive care.</td>
<td>Permanently discontinue ipatasertib</td>
</tr>
</tbody>
</table>

### Nausea

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide supportive care as needed.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron and prochlorperazine. Consider Olanzapine for patients with delayed/refractory/anticipatory nausea.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold ipatasertib</td>
<td>Resume Ipatasertib reduced by 1 dose level if toxicity resolves to Grade ( \leq 1 ) or baseline within 4 weeks</td>
</tr>
<tr>
<td>Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron and prochlorperazine. Consider Olanzapine for patients with delayed/refractory/anticipatory nausea.</td>
<td>Exception: Nausea lasting ( \leq 72 ) hours</td>
</tr>
<tr>
<td>Resume Ipatasertib reduced by 1 dose level if toxicity resolves to Grade ( \leq 1 ) or baseline within 4 weeks</td>
<td>If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
</tr>
<tr>
<td>Exception: Nausea lasting ( \leq 72 ) hours</td>
<td>Permanently discontinue if toxicity does not improve to Grade ( \leq 1 ) or baseline within 4 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently discontinue ipatasertib</td>
<td>Permanently discontinue ipatasertib</td>
</tr>
</tbody>
</table>
Vomiting

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• Provide supportive care as needed.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Provide maximum supportive care as needed per local guidelines, with a</td>
</tr>
<tr>
<td></td>
<td>minimum of two anti-emetics, including ondansetron and prochlorperazine.</td>
</tr>
<tr>
<td></td>
<td>Consider Olanzapine for patients with delayed/refractory/anticipatory</td>
</tr>
<tr>
<td></td>
<td>vomiting.</td>
</tr>
<tr>
<td></td>
<td>• Consider intravenous Hydration</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• Hold ipatasertib</td>
</tr>
<tr>
<td></td>
<td>• Provide maximum supportive care as needed per local guidelines, with a</td>
</tr>
<tr>
<td></td>
<td>minimum of two anti-emetics, including ondansetron and prochlorperazine.</td>
</tr>
<tr>
<td></td>
<td>• Consider Olanzapine for patients with delayed/refractory/anticipatory</td>
</tr>
<tr>
<td></td>
<td>vomiting.</td>
</tr>
<tr>
<td></td>
<td>• Provide intravenous Hydration</td>
</tr>
<tr>
<td></td>
<td>• Resume Ipatasertib reduced by 1 dose level if toxicity resolves to Grade</td>
</tr>
<tr>
<td></td>
<td>≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td></td>
<td>• Exception: Vomiting lasting ≤72 hours</td>
</tr>
<tr>
<td></td>
<td>• If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue if toxicity does not improve to Grade ≤1 or</td>
</tr>
<tr>
<td></td>
<td>baseline within 4 weeks.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• Permanently discontinue ipatasertib</td>
</tr>
</tbody>
</table>

Table 3.2 Suggested Treatment Modifications for Hematological Toxicity Possibly Related to Ipatasertib

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1, or Grade 2 or 3</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 4 or Febrile Neutropenia</td>
<td>• Hold ipatasertib and monitor weekly until ANC ≥1500/µL.</td>
</tr>
<tr>
<td></td>
<td>• Resume Ipatasertib based on the following recovery times:</td>
</tr>
<tr>
<td></td>
<td>o ≤1 week: No change</td>
</tr>
<tr>
<td></td>
<td>o &gt;1 week: Ipatasertib may be reduced by 1 dose level</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue ipatasertib if persists for &gt;4 weeks without</td>
</tr>
<tr>
<td></td>
<td>recovery to ANC ≥1500/µL. Refer to hematologist for evaluation</td>
</tr>
<tr>
<td></td>
<td>including assessment of possible MDS/AML</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.3 Suggested Treatment Modifications for Hepatic Toxicity Possibly Related to Ipatasertib

<table>
<thead>
<tr>
<th>AST/ALT Elevation (And Bilirubin &lt; 1.5 ULN)</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1, or Grade 2</td>
<td>No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold ipatasertib and monitor weekly till resolves to Grade ≤1 or baseline</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Monitor LFTs weekly till resolves to Grade ≤1 or baseline</td>
</tr>
<tr>
<td></td>
<td>Resume ipatasertib reduced by 1 dose level if toxicity resolves to Grade ≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Exception: Increase in indirect bilirubin indicative of Gilbert’s syndrome</td>
</tr>
<tr>
<td></td>
<td>If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
</tr>
<tr>
<td></td>
<td>Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks</td>
</tr>
</tbody>
</table>
### Bilirubin >1.5 ULN (regardless of AST/ALT levels)

<table>
<thead>
<tr>
<th>Grade 1, or Grade 2</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No requirement for dose interruption or dose reduction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold ipatasertib</td>
<td></td>
</tr>
<tr>
<td>Monitor LFTs weekly till resolves to Grade ≤1 or baseline within 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Resume ipatasertib reduced by 1 dose level if toxicity resolves to Grade ≤1 or baseline within 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Exception: Increase in indirect bilirubin indicative of Gilbert’s syndrome</td>
<td></td>
</tr>
<tr>
<td>If the same Grade 3 toxicity, recurs, reduce by 1 dose level.</td>
<td></td>
</tr>
<tr>
<td>Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently discontinue ipatasertib</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 3.4 Suggested Treatment Modifications for Hyperglycemia Possibly Related to Ipatasertib**

<table>
<thead>
<tr>
<th>Hyperglycemia</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>The patient should receive education on a diabetic diet and life-style modification.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>The patient should receive education on a diabetic diet, life-style modification, and consider home glucose monitoring.</td>
</tr>
<tr>
<td></td>
<td>Oral anti-diabetic medications (e.g., metformin) may be started at the discretion of the investigator.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>The patient should adopt a diabetic diet and initiate home glucose monitoring.</td>
</tr>
<tr>
<td></td>
<td>Start oral anti-diabetic medications (e.g., metformin).</td>
</tr>
<tr>
<td></td>
<td>Consider interruption of ipatasertib</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Interrupt ipatasertib dosing until fasting hyperglycemia resolves to Grade 2 or better.</td>
</tr>
</tbody>
</table>
Hyperglycemia

Prophylaxis

- The patient should receive education on a diabetic diet and life-style modification.

- Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin).

- The patient should adopt a diabetic diet and initiate home glucose monitoring.

- If the fasting hyperglycemia resolves to Grade 2 or better within 3 days, ipatasertib may be resumed at the previous dose level.

- If fasting glucose levels do not recover to Grade 2 or better within 3 days, ipatasertib should be reduced by one dose level when treatment is restarted.

- If Grade ≥ 3 fasting hyperglycemia recurs within 14 days the dose of ipatasertib should be reduced by one dose level when treatment is restarted.

Grade 4

- Interrupt ipatasertib dosing until fasting hyperglycemia resolves to Grade 2 or better.

- Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin).

- The patient should adopt a diabetic diet and initiate home glucose monitoring.

- Upon recovery of fasting glucose levels to Grade 2 or better, ipatasertib should be reduced by one dose level when treatment is restarted.

- If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib.

Table 3.5 Suggested Treatment Modifications for Rash Possibly Related to Ipatasertib

<table>
<thead>
<tr>
<th>Rash</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>- No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td></td>
<td>- Consider topical corticosteroids.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>- No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td></td>
<td>- Treat rash with topical corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>- Consider treatment of rash with oral corticosteroids.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>- Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant.</td>
</tr>
<tr>
<td></td>
<td>- Treat rash with topical and systemic corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>- Consider dermatological consultation and skin biopsy.</td>
</tr>
</tbody>
</table>
Rash

- If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose.
- If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.

Table 3.6 Suggested Treatment Modifications for Other Toxicity Possibly Related to Ipatasertib*

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Ipatasertib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1, or 2</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• Hold Ipatasertib</td>
</tr>
<tr>
<td></td>
<td>• Resume Ipatasertib reduced by 1 dose level if toxicity resolves to Grade ≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• Permanently discontinue Ipatasertib</td>
</tr>
</tbody>
</table>

*Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only without clinical significance (e.g., elevation of ALP) Study treatment may continue without interruption and/or dose reduction at the discretion of the investigator.

6.3 Management for Palbociclib and Ipatasertib Therapy Toxicity (Arm C)

Dose modifications for ipatasertib therapy are provided in Table 2 and Table 3. Dose modifications for palbociclib therapy are provided in Table 4 and Table 5, and essentially reflect the recommendations as per FDA label. Please note, both ipatasertib and palbociclib may be withheld for overlapping toxicities, such as diarrhea, per respective dose modification tables.
Diarrhea is potentially an overlapping toxicity with palbociclib and ipatasertib therapy. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle, and investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgment. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with water and electrolyte-containing liquids. Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed.

Patients may hold the ipatasertib for up to 28 consecutive days to recover from toxicity or an adverse event related to the study drug. There is no duration limit for holding palbociclib and/or endocrine therapy. If the ipatasertib is discontinued at any time during the study, patients may have the option of continuing standard endocrine therapy with/without palbociclib. Alternatively, if the standard endocrine therapy with/without palbociclib is discontinued at any time during the study based on investigator discretion, patients may have the option of continuing ipatasertib. Please note the guidelines are suggested recommendations (not mandatory), and investigator should treat patient considering safety and tolerability.

Table 4. Dose modifications for palbociclib therapy

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Palbociclib Dose (mg), for 3 weeks, every 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Dose</td>
<td>125</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>100</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>75</td>
</tr>
</tbody>
</table>
### Table 5.1. Treatment Modifications for Gastrointestinal Toxicity Possibly Related to Palbociclib

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Grade 1</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Hold treatment; assess patient weekly (biweekly for Grade 4 toxicity)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• If recovery to ≤ Grade 1 delays next dose by only one week, treatment resumes without dose reduction.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• If recovery to ≤ Grade 1 delays next dose by 2 or 3 weeks, treatment resumed at reduced dose.</td>
</tr>
<tr>
<td></td>
<td>• If recovery to ≤ Grade 1 requires more than a 3-week delay, treatment permanently discontinued.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vomiting</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Grade 1</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Hold treatment; assess patient weekly (biweekly for Grade 4 toxicity)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• If recovery to ≤ Grade 1 delays next dose by only one week, treatment resumes without dose reduction.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• If recovery to ≤ Grade 1 delays next dose by 2 or 3 weeks, treatment resumed at reduced dose.</td>
</tr>
<tr>
<td></td>
<td>• If recovery to ≤ Grade 1 requires more than a 3-week delay, treatment permanently discontinued.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Grade 1</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Hold treatment; assess patient weekly (biweekly for Grade 4 toxicity)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• If recovery to ≤ Grade 1 delays next dose by only one week, treatment resumes without dose reduction.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• If recovery to ≤ Grade 1 delays next dose by 2 or 3 weeks, treatment resumed at reduced dose.</td>
</tr>
<tr>
<td></td>
<td>• If recovery to ≤ Grade 1 requires more than a 3-week delay, treatment permanently discontinued.</td>
</tr>
</tbody>
</table>


## Treatment Modifications for Hematological Toxicity Possibly Related to Palbociclib

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Grade 1</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>• Day 1 of cycle: hold palbociclib; assess patients weekly. When recovered</td>
</tr>
<tr>
<td></td>
<td>to ≤ Grade 2, treatment may resume without dose reduction.</td>
</tr>
<tr>
<td></td>
<td>• Day 15 of cycle or any other day of cycle besides Day 1 (if labs checked):</td>
</tr>
<tr>
<td></td>
<td>continue palbociclib.</td>
</tr>
<tr>
<td></td>
<td>• Consider addition of G-CSF (as per investigator discretion).</td>
</tr>
<tr>
<td></td>
<td>• Consider dose reduction in cases of prolonged (&gt;1 week) recovery from</td>
</tr>
<tr>
<td></td>
<td>Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of</td>
</tr>
<tr>
<td></td>
<td>subsequent cycles (as per investigator discretion).</td>
</tr>
<tr>
<td>Grade 3 with fever ≥38.5 °C and/or infection</td>
<td>• Hold palbociclib; assess patients weekly. When recovered to ≤ Grade 2,</td>
</tr>
<tr>
<td></td>
<td>treatment may resume at next lower dose.</td>
</tr>
<tr>
<td></td>
<td>• Consider addition of G-CSF (as per investigator discretion).</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• Hold palbociclib; assess patients weekly. When recovered to ≤ Grade 2,</td>
</tr>
<tr>
<td></td>
<td>treatment may resume at next lower dose.</td>
</tr>
<tr>
<td></td>
<td>• Consider addition of G-CSF (as per investigator discretion).</td>
</tr>
</tbody>
</table>

## Thrombocytopenia

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>• No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• Day 1 of cycle: hold palbociclib; assess patients weekly. When recovered</td>
</tr>
<tr>
<td></td>
<td>to ≤ Grade 2, treatment may resume without dose reduction.</td>
</tr>
<tr>
<td></td>
<td>• Day 15 of cycle or any other day of cycle besides Day 1 (if labs checked):</td>
</tr>
<tr>
<td></td>
<td>continue palbociclib.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• Hold palbociclib; assess patients weekly. When recovered to ≤ Grade 2,</td>
</tr>
<tr>
<td></td>
<td>treatment may resume at next lower dose.</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue palbociclib if persists for &gt;4 weeks without</td>
</tr>
<tr>
<td></td>
<td>recovery to platelets ≥75,000/µL. Refer to hematologist for evaluation</td>
</tr>
<tr>
<td></td>
<td>including assessment of possible MDS/AML.</td>
</tr>
</tbody>
</table>

## Anemia

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Grade 1 or 2
- No requirement for dose interruption or dose reduction

Grade 3
- Day 1 of cycle: hold palbociclib; assess patients weekly. When recovered to ≤ Grade 2, treatment may resume without dose reduction.
- Day 15 of cycle or any other day of cycle besides Day 1 (if labs checked): continue palbociclib.

Grade 4
- Hold palbociclib; assess patients weekly. When recovered to ≤ Grade 2, treatment may resume at next lower dose.

### Treatment Modifications for Hepatic Toxicity Possibly Related to Palbociclib

<table>
<thead>
<tr>
<th>AST/ALT Elevation (Bilirubin)</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 1.5 ULN</strong></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 1</td>
<td>- No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>- Hold treatment; assess patient weekly (biweekly for Grade 4 toxicity)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>- If recovery to ≤ Grade 1 delays next dose by only one week, resume treatment without dose reduction.</td>
</tr>
<tr>
<td></td>
<td>- If recovery to ≤ Grade 1 delays next dose by 2 or 3 weeks, resume treatment at reduced dose.</td>
</tr>
<tr>
<td></td>
<td>- If recovery to ≤ Grade 1 requires more than a 3-week delay, discontinue treatment permanently.</td>
</tr>
<tr>
<td><strong>&gt;1.5 ULN</strong></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 1</td>
<td>- No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>- Hold treatment; assess patient weekly</td>
</tr>
<tr>
<td>Grade 4</td>
<td>- After recovery to ≤ Grade 1, resume treatment at reduced dose.</td>
</tr>
<tr>
<td></td>
<td>- Permanently discontinue palbociclib</td>
</tr>
</tbody>
</table>

### Treatment Modifications for Other Toxicity Possibly Related to Palbociclib

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1, or Grade 2</td>
<td>- No requirement for dose interruption or dose reduction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>- Hold palbociclib</td>
</tr>
<tr>
<td></td>
<td>- Resume palbociclib reduced by 1 dose level if toxicity resolves to Grade ≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td></td>
<td>- Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks</td>
</tr>
<tr>
<td>Grade 4</td>
<td>- Permanently discontinue palbociclib</td>
</tr>
</tbody>
</table>
6.4 Management for Endocrine Therapy Toxicity

Dose modifications for endocrine therapy can be performed per standard practice or institutional guidelines.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period.
- AE reporting period, including signs or symptoms associated with Metastatic Hormone Receptor Positive/HER2 negative metastatic breast cancer (TAKTIC) that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated
intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

### Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization (Please refer to Section 7.3d for additional details).
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

### 7.1 Expected Toxicities

**Ipatasertib**

Most common adverse reactions with ipatasertib include diarrhea, nausea, vomiting, asthenia, fatigue, hyperglycemia, dehydration, decreased appetite, rash, rash maculopapular and toxic skin eruption (Saura C, 2017). Fatal or life-threatening adverse events are considered unexpected for Ipatasertib.
Palbociclib

Most common adverse reactions with palbociclib include neutropenia, infections, leukopenia, anemia, thrombocytopenia, fatigue, nausea, vomiting, diarrhea, stomatitis, alopecia, rash, decreased appetite, asthenia, and pyrexia (as per FDA label).

7.2 Adverse Event Characteristics

For expedited reporting purposes only:

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

Attribution of the AE:

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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

7.3 Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complication treating investigators must immediately notify the PI. 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 FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study
discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

7.3.1 Eliciting Adverse Events
A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

7.3.2 Specific Instructions for Recording Adverse Events
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms
If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). 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.

b. 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 “Unexplained Death”.

c. 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 trial 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 important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. 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 subject 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. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass 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
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.
f. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s law:
  - Treatment-emergent ALT or AST \( > 3 \times \text{ULN} \) in combination with total bilirubin \( > 2 \times \text{ULN} \)
  - Treatment-emergent ALT or AST \( > 3 \times \text{ULN} \) in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Ipatasertib Events of Special Interest are:

- Grade \( \geq 3 \) fasting hyperglycemia
- Grade \( \geq 3 \) hepatotoxicity
- Grade \( \geq 3 \) ALT/AST elevations
- Grade \( \geq 2 \) colitis/enterocolitis
● Grade ≥ 3 diarrhea
● Grade ≥ 3 rash
● Grade ≥ 2 pneumonitis

g. **Other Special Situations Reports**
The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:
   - Data related to the Product usage during breastfeeding
   - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
   - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

h. **Product Complaints**
A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

### 7.4 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE 5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

---

**Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**
Grade | Severity
---|---
1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living a
3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living b,c
4 | Life-threatening consequences or urgent intervention indicated d
5 | Death related to adverse event d

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE 5.0 which can be found at:

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. All Grade 4 and 5 events must be reported as serious adverse events

7.5 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The Sponsor will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.
The sponsor will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

**Additional Reporting Requirements for IND Holders:**

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

**7 Calendar Day Telephone or Fax Report:**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of Ipatasertib. An unexpected adverse event is one that is not already described in the Ipatasertib Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

**15 Calendar Day Written Report**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Ipatasertib. An unexpected adverse event is one that is not already described in the Ipatasertib investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND
concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

**FDA fax number for IND Safety Reports:**
Fax: 1 (800) FDA 0178

**All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:**
Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

And the Sponsor will be responsible for the distribution of safety information to Site IRB.

**For questions related to safety reporting, please contact Genentech Drug Safety:**
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

**AGGREGATE REPORTS**
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

The Sponsor will forward a copy of the Final Study Report to Genentech upon completion of the Study.

**Case Transmission Verification of Single Case Reports**
The parties will verify that all single case reports have been adequately received by Genentech via the sponsor e-mailing Genentech a Quarterly line-listing documenting single case reports sent by the sponsor to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the ‘Activation Package’.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by sponsor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

**Exchange OF SINGLE CASE REPORTS**

The sponsor will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067  
Email: usds_aereporting-d@gene.com

All Product Complaints **without** an AE should call via:  
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Investigators must report all the above mentioned single case reports adequately to Genentech on a within one (1) business day of the awareness date.

The sponsor will forward quarterly listings of non-serious AEs originating from the Study to Genentech.
MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator’s assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
  - Adding to the original MedWatch 3500A report and submitting it as follow-up
  - Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
  - Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download
**Post-Study Adverse Events**

The investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (quarterly) to ensure successful transmission of Single case reports.

**7.6 Reporting to Hospital Risk Management**

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

**7.7 Routine Adverse Event Reporting**

All Adverse Events must be reported in routine study data submissions to the PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

**7.8 Study Close-Out**

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study and to Genentech Drug Safety CTV oversight mail box at:

ctvist_drugsafety@gene.com

**7.9 Queries**

Queries related to the Study will be answered by Sponsor. However, responses to all safety queries from regulatory authorities or for publications will be discussed and
coordinated between the Parties. The Parties agree that Genentech shall have the
final say and control over safety queries relating to the Product. Sponsor agrees that
it shall not answer such queries from regulatory authorities and other sources
relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests
for information or review of data are met. The Parties will clearly indicate on the request the
reason for urgency and the date by which a response is required.

7.10 Signal Management and Risk Management
Genentech is responsible for safety signal management (signal detection and/or
evaluation) for their own Product. However, it is agreed that Sponsor of the Study,
will be primarily responsible for assessment of the benefit-risk balance of the
Study.

If sponsor of the study issues a safety communication relevant for Genentech (i.e., a
safety issue that notably impacts the benefit-risk balance of the Study and / or
triggers any changes to the Study) this will be sent to Genentech within five (5)
business days of its internal approval.

As needed, Genentech will reasonably assist sponsor of this study with signal and
risk management activities related to the Product within the Study.

Genentech will also provide sponsor of this study with any new relevant
information that may modify or supplement known data regarding the Product (e.g.,
relevant Dear Investigator Letter).

7.11 Compliance with Pharmacovigilance Agreement/Audit
The Parties shall follow their own procedures for adherence to AE reporting timelines.
Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE
report timeliness in accordance with its own procedures. The Parties agree to provide written
responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.5.1.

8.1 Ipatasertib

Ipatasertib drug product is a film-coated, greyish-yellow (100mg)/brownish-pink (200mg), oval, immediate-release tablet. It is supplied as 100mg and 200mg tablets. The inactive ingredients in ipatasertib tablets are microcrystalline cellulose, pregelatinized maize starch, croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate, Opadry II Yellow film coat (100mg), and Opadry II Pink film coat (200 mg). Ipatasertib should ideally be stored at room temperate (15-25°C), however, it can be stored between 2-25°C, but not above 25°C (77°F).

A sufficient amount of ipatasertib should be provided to the patient to last for up to one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib
and their medication diaries to each study visit. Ipatasertib should be stored between 59°F to 86°F (15°C to 30°C) in the original container that includes the desiccant.

Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib may be taken with or without food. If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. Ipatasertib should be taken at approximately the same time each day.

8.2 Standard Hormone Therapy and Palbociclib

Standard hormone therapy and palbociclib will be provided by local pharmacy, as per standard of care. All 3 aromatase inhibitors (anastrozole, letrozole, and exemestane) will be administered as oral medication. Fulvestrant will be administered as intra-muscular injection. Ipatasertib will generally be administered first. The standard drugs may be administered per MD discretion. No specific time interval required between administration of ipatasertib and standard hormone therapy or palbociclib.

Aromatase inhibitor as well as palbociclib should be taken with food at approximately the same time each day. Fasting is not required. All 3 aromatase inhibitors (anastrozole, letrozole, and exemestane) are to be taken once daily. No specific preference on time of day. If the patient vomits or misses a dose, an additional dose should not be taken, and the next prescribed dose should be taken at the usual time. Aromatase inhibitor as well as palbociclib should be swallowed whole (not chewed, crushed or opened prior to swallowing) with a glass of water.
9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

There is a critical need to glean further insight into the molecular pathways that govern response and resistance to the CDK4/6 inhibitors in patients with HR+ metastatic breast cancer. While acquired alterations in RB1 have been identified in multiple studies (Condorelli R, 2017; Turner NC, 2018; Wander S, 2018), these events provide a plausible molecular explanation for only a minority of the resistant patient population. Our own work has implicated a variety of heterogeneous molecular alterations in resistant patients, including AKT1, FGFR2, ERBB2, AURKA, and RAS family proteins, among others (Wander ASCO 2018).

We will obtain tissue and blood samples from patients enrolling in this study to further our understanding of the molecular alterations that may 1) characterize resistance in post-progression on CDK4/6-based therapy, and 2) predict which patients may be best suited for AKT-directed therapy in the post-progression setting. Solid tumor biopsies will be optional (high encouraged) at enrollment and at the time of progression. These tumor specimens will be utilized for:

1) Immunohistochemical analysis (IHC) of various proteins of interest including, but not limited to AKT/pAKT and related molecular readouts (including S6/pS6), Rb/pRb, and Ki67

2) Next-generation sequencing (NGS) including, but not limited to, targeted sequencing of known cancer-related genes (MGH SNAPSHOT), whole exome sequencing, RNA transcriptome analysis, and single-cell RNA sequencing

The specimen collection details are outlined in Appendix. The blood specimens will also be utilized for NGS, specifically including, but not limited to, molecular analysis of cell-free
circulating tumor DNA (cfDNA), targeted sequencing of cancer-related genes via cfDNA, and
(when cfDNA content and purity allow) whole exome sequencing. We will utilize our
longstanding collaboration with collaborators at the Broad Institute of MIT and Harvard to
perform sequencing and subsequent computational analysis of NGS results. In addition, blood
would be collected for PK analysis, as outlined in study calendar.

The mechanism of ipatasertib-induced diarrhea is not well understood, though inflammation may
play a role. To evaluate role of inflammation, stool collection for assessment of fecal leukocytes
and calprotectin levels will be obtained in patients experiencing diarrhea during study (van
Rheenen PF, 2010), and analyzed by Quest Diagnostics as per standard procedures (test code
3930 and 16796). In addition, all patients will complete a validated IBS questionnaire (Roalfe
AK, 2018). The specimen collection schedule is outlined in Study Calendar.

10. STUDY CALENDAR

<table>
<thead>
<tr>
<th>Procedures/Assessments</th>
<th>Study Day (assessment window in days)</th>
<th>Cycle 1 (1-28)</th>
<th>Cycle 2 (1-28)</th>
<th>Subsequent cycles (1-28)</th>
<th>End of Treatment</th>
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<td>Day 1b (±3)</td>
<td>Day 8b (±3)</td>
<td>Day 15b (±3)</td>
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<td>Within 14 days (+ 7)</td>
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<td>Cycle 1 (1-28)</td>
<td>Cycle 2 (1-28)</td>
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<td>Day 8&lt;sup&gt;b&lt;/sup&gt; (±3)</td>
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<sup>a</sup> Day -28 to -1

<sup>b</sup> Day ±3

<sup>c</sup> Lab test ±3

Within 14 days (+ 7)
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<tr>
<td>Tissue collection&lt;sup&gt;h&lt;/sup&gt;</td>
<td>X&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stool collection&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fulvestrant (arm A; arm C)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aromatase inhibitor (arm B)</td>
<td></td>
<td></td>
<td></td>
<td>Orally once daily</td>
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</tr>
<tr>
<td>Palbociclib (arm C)&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Orally once daily, three week on and one week off (days 8-28)&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ipatasertib administration (arms A and B)&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Orally once daily (days 1-28)&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ipatasertib administration (arm C)&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Orally once daily, three week on and one week off (days 1-21)&lt;sup&gt;j&lt;/sup&gt;</td>
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</table>

<sup>a</sup> All screening assessments should be completed 28 days prior to the first dose.
<sup>b</sup> All on treatment assessments to be performed pre-dose on scheduled visit days unless otherwise indicated. During in-clinic visits, treatment dose should be given in clinic.
<sup>c</sup> HbA1c during screening. CBC with diff, Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, fasting glucose (approximately 4 hours fasted), LDH, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT
ALT, sodium. Pregnancy test (serum) during screening, Cycle 1 Day 1 and Day 1 of every even cycle thereafter (cycle 2, 4, 6, 8, 10, 12) for patients on gonadotropin-releasing hormone agonist. Estradiol, LH, and FSH testing to be performed at Screening and only for patients who are ≤ 60 years old.

d. 12-lead ECG to be performed at screening (triplicate), Cycle 1 Day 1 (single), Cycle 1 Day 15 (single), and every 2 cycles (cycle 3, 5, etc; single), and at End of Treatment (single).

e. Tumor assessments to be performed at Screening and then every 8 weeks till 6 months (Week 24), and then every 12 weeks. For patients who achieve a CR or PR, a confirmation scan must be repeated at least 4 weeks after the first documented response. Enrolled patients with history of stable brain metastases and baseline non-target lesion (as per RECIST) should have brain imaging in parallel with systemic imaging (modality choice as per treating investigator) for evaluation of non-target lesions in the brain. Otherwise brain imaging is as per discretion of treating investigator. Bone scan should be performed at Screening only (if a patient has PET/CT with bone window during screening, then bone scan requirement may be omitted). If patient has a positive bone scan or PET/CT (findings suggestive of bone mets), repeat bone scan (or PET/CT) should be obtained every 12-24 weeks (investigator discretion). Scans can be performed up to 7 days before the scan review visit.

f. Please see appendix D for instructions on collection of blood samples. Blood samples for PK analysis will be performed at following time points:
   i. For all patients enrolled on Arm C in the safety run-in phase and in approximately 12 patients in the expansion cohort:
      • Cycle 1 Day 1: 0 (pre-dose)
      • Cycle 1 Day 15 (+/- 3 days): 0 (pre-dose), 30 min (+/- 10 min), 1 h (+/- 15 min), 2 h (+/- 30 min), 4 h (+/- 30 min) post dose, 6 h (+/- 30 min) post dose.
      • Cycle 2 Day 15 (+/- 3 days): 0 (pre-dose), 30 min (+/- 10 min), 1 h (+/- 15 min), 2 h (+/- 30 min) and 4 h (+/- 30 min) post dose, 6 h (+/- 30 min) post dose.
   ii. For all patients enrolled on Arms A or B, a pre-dose PK sample will be collected on Cycle 1 Day 1 and Cycle 1 Day 15 (+/- 3 days)
   iii. A PK sample will also be taken at time points when an unscheduled ECG assessment is conducted or an unexpected adverse event is experienced by a patient on any treatment Arm.
   iv. Additionally, investigators may obtain blood samples for PK analysis at the time(s) that significant AEs and SAEs occur that are considered potentially related to the study agent(s).
   v. If the patient has dosing holidays prior to PK visit, then the PK sampling can be rescheduled to another day within the cycle (Day 15 to 21) after at least 3 days of uninterrupted dosing prior to the visit for PK sampling.

g. Blood sample for ctDNA analysis to be collected at Screening, Cycle 1 Day 1, Cycle 1 Day 15, and every 2 cycles (cycle 3, 5, etc), and at End of Treatment. Please see appendix D for instructions on collection of blood samples.

h. Archival tumor sample (fresh tumor biopsy if insufficient specimen): 20 unstained slides (minimum of 5 slides), or 1 block (preferred). If subject has accessible tumor and
consents to the optional pre-treatment biopsy collection, at least 3 core-biopsies will be collected in place of archival tissue.

i. In patients with diarrhea (any grade), fecal specimen (1-2 times/diarrheal episode) to be collected in stool container.

j. The schedule might change during conduct of the study, depending on safety, tolerability and PKs. Ipatasertib and palbociclib dosing can occur at night, per treating physician discretion.

k. If subject has accessible tumor and consents to the optional post-treatment biopsy collection, at least 3 core-biopsies will be collected.

11. MEASUREMENT OF EFFECT

11.1 Safety and Toxicity

Toxicity-related end points can be found and explained in dose reductions, Section 6.

11.2 Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Disease-Free Survival (PFS) is defined as the time from randomization (or registration) to evidence of disease recurrence or death due to any cause. Participants alive without disease recurrence are censored at date of last evaluation.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study. 
Note: If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DF/HCC DSMC will offer recommendations regarding whether or not to suspend the study.

Information to be provided to the DF/HCC DSMC may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.
13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Standard 3+3 phase-1 design will be utilized in this trial for arm C. The details are outlined in section 5.1. Briefly, a minimum of 3 evaluable patients will be entered at first dose level. If 1 out of the first 3 patients enrolled experiences a dose-limiting toxicity (DLT), 3 additional patients will be enrolled to that dose level. If no more than 1 patient in 6 experiences a DLT, dose escalation will continue to next dose-level. If 2 or more patients at any given dose level experience a DLT, dose escalation will stop and the maximum tolerated dose (MTD) will be defined. We will not exceed the R2PD of palbociclib (125 mg, for 3 weeks, every 28 days) and/or ipatasertib (400 mg days 1-21, every 28 days). Once MTD/R2PD is determined there will be a dose-expansion cohort (N = approximately 15) to confirm safety profile and evaluate preliminary evidence of efficacy to guide future development of the drug combination of triplet therapy. Similarly, in arms A and B, we will conduct a dose-expansion cohort (N = approximately 15) to confirm safety profile and evaluate preliminary evidence of efficacy to guide future development of the drug combination of doublet therapy.

While we do not anticipate significant overlapping toxicities between endocrine therapy and ipatasertib and there will not be no dose-escalation cohort(s) for the doublet arms (arm A and arm B), we will monitor for DLTs, and consider dose reduction if needed. We will initially enroll 6 patients in arm A, and if there are no more than 1 DLT, we will proceed towards enrollment of approximately 9 other patients (total N = approximately 15). A DLT rate of more than 33% will be considered as too toxic for future development of the drug combination of doublet therapy with ipatasertib and aromatase inhibitor. The same DLT principle will be followed for arm B (i.e
we will enroll initially enroll 6 patients in arm B, and if there are no more than 1 DLT, we will
proceed towards enrollment of approximately 9 other patients. A DLT rate of less than 33% will
be considered as success for future development of the drug combination of doublet therapy with
ipatasertib and fulvestrant).

13.2 Sample Size, Accrual Rate and Study Duration

Approximately 15 patients each will be enrolled in arm A and B of the clinical trial. Depending
on the occurrence of a ≥ Grade 3 treatment related toxicity and DLT, it is expected that about 15-
30 patients will be required in Arm C this trial to determine the MTD of Fulvestrant with
Palbociclib and Ipatasertib Overall, approximately 75 patients will be enrolled to the study.

13.3 Analysis of Primary Endpoints

Safety and tolerability, according to the CTCAE version 5 as determined by the treating
investigator, is the primary endpoint for cohort A and B. All patients who receive at least one
dose of ipatasertib will be considered evaluable for the safety and tolerability endpoint.

DLT is the primary endpoint for Cohort C. Analyses of DLT will be based on the DLT-evaluable
set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed per
cohort, overall and by dose level, for patients enrolled in Phase 1b.

13.4 Analysis of Secondary Endpoints

PFS and ORR are secondary endpoints in the study. ORR is defined as the proportion of patients
with a confirmed CR or PR per Investigator’s assessment per RECIST v1.1. Confirmed
responses are those that persist on repeat tumor assessments for at least 4 weeks after initial
documentation or response. Otherwise, the patient will be counted as a non-responder in the
assessment of ORR. Patients with inadequate data for tumor assessment such as no baseline or
follow-up assessments, will be considered non-responders in the ORR assessment. The two-
sided 95% CIs for ORR will be calculated. Progression-Free Survival (PFS) is defined as the
time from the first dose of study treatment to the date of progression by RECIST v1.1 or death
due to any cause, whichever occurs first. PFS data will be censored on the date of the last
adequate tumor assessment for patients who do not have an event (PD or death) for patients who
start new anti-cancer treatment prior to an event, or for patients with an event after 2 or more
missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not
have any post-baseline tumor assessments will be censored on the start date unless death
occurred on or before the time of the second planned tumor assessment in which case the death
will be considered an event. Overall survival (OS) is defined as the time from the first dose of
study treatment to the date of death. Patients without an event (death) will be censored at the date
of last contact.

13.5 Reporting and Exclusions

Patients who do not start therapy after signing informed consent will be excluded and their spot
in the trial replaced.

13.5.1 Electronic Case Report Forms (eCRFs)

An eCRF is required and must be completed for each enrolled patient. It is the Investigator’s
responsibility to ensure the completion and to review and approve all eCRFs. They must be
signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. The Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. When source documents are the hospital or the physician’s chart, the information collected on the eCRFs must match those charts. When a portion of source documents for a given study site are the eCRFs, the Investigator must agree which items will be recorded in the source documents and for which items the eCRF will stand as the source document.

Corrections to the eCRF must be initialed and dated by the person making the correction (ICH E6 4.9.3).

13.5.2 Record Retention

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, and medication inventory records must be retained by the Investigator for at least 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. Records should be retained by the Investigator per ICH guidelines, per local regulations, or as specified in the clinical study agreement, whichever is longer. No study records shall be destroyed without prior authorization from the pharmaceutical companies.
REFERENCES


### APPENDIX A PERFORMANCE STATUS CRITERIA

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td><strong>Descriptions</strong></td>
</tr>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterility Code</td>
<td>Description</td>
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</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
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<tr>
<td></td>
<td>Disabled, requires special care and assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td>Very sick, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>4</td>
<td>Moribund, fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

NCI Protocol #: DF/HCC Protocol #: 19-086
Protocol Version Date: 06 May 2021
APPENDIX B

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A4. Strong CYP3A inhibitors and CYP3A substrates with narrow therapeutic window should be avoided.

Medications to be used with caution:

- Strong CYP3A4/5 inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir,itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and/or grapefruit juice.
- Strong CYP3A4/5 inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John’s wort or hyperforin.
- CYP3A4/5 substrates with a narrow therapeutic index, such as, but not limited to, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine.

This is not a comprehensive list. Please refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

- [http://medicine.iupui.edu/clinpharm/ddis/table.aspx](http://medicine.iupui.edu/clinpharm/ddis/table.aspx) or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
APPENDIX C DIARRHEA QUESTIONNAIRE

BIRMINGHAM IBS SYMPTOM QUESTIONNAIRE
The following questions ask you about your abdominal and bowel symptoms. When we use the word abdomen we mean belly/tummy. Some of the questions ask about passing a stool. By this we mean going to the toilet for a reason other than to urinate (pass water). All of these questions refer to the last 4 weeks.
Please tick one box for each statement.

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
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<tbody>
<tr>
<td>1. During the last 4 weeks, how often have you had discomfort or pain in your abdomen?</td>
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<td>2. How often have you been troubled with loose, mushy or watery bowel motions during the last 4 weeks?</td>
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<td>3. How often during the last 4 weeks have you been troubled with diarrhoea?</td>
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<td>4. During the last 4 weeks how often have you been troubled by hard bowel motions?</td>
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<tr>
<td>5. During the last 4 weeks how often have you felt the need to strain to pass a motion (stool)?</td>
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<td>6. During the last 4 weeks how often have you been troubled by constipation?</td>
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<tr>
<td>7. During the last 4 weeks how often did you experience pain or discomfort in your abdomen after eating?</td>
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<td>8. How often has your abdominal pain prevented you from sleeping, or woken you during the night during the last 4 weeks?</td>
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<tr>
<td>9. During the last 4 weeks how often have you leaked or soiled yourself?</td>
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<tr>
<td>10. How often during the last 4 weeks have you suffered from a feeling of urgency (feeling that you must immediately rush to the toilet to pass a stool)?</td>
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<tr>
<td>11. How often have you passed mucus or slime in your stools over the last 4 weeks?</td>
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</table>

Requests for permission to utilise the Birmingham IBS symptom questionnaire should be sent to one of the following:
Andrea Roaf/C/lesley Roberts/Sue Wilson, Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
APPENDIX D BIOASSAY TEMPLATES

Blood Collection/Processing Workflow and Procedures for ctDNA

Step #1 - Blood Draw (in Clinic)

a) 20ml (or 2 10 ml Cell-Free DNA BCT Streck tubes) is collected by any standard phlebotomy technique from a peripheral access point or from a central line by trained personnel.

b) Tubes are inverted about 10 times immediately after collection.

c) Samples are the prepared for transportation to the laboratory or processing site.

Step #2 - Plasma Processing (in Laboratory)

a) Perform this step once for each patient: transfer 1 mL whole blood with a pipette to a pre-labeled 2 mL cryogenic vial, round bottom, self-standing

b) Streck tubes are centrifuged at room temperature for 10 min at 1600 (±150) g.

c) After centrifugation, remove tubes from centrifuge and transfer supernatant of the Streck tubes to one fresh 10 ml polypropylene centrifuge tube without disturbing the cellular layer using a disposable serological pipette or disposable bulb pipette.

d) Centrifuge the plasma in the 10 ml centrifuge tube at room temperature for 10 min at 3000 (±150) g.

e) After centrifugation, remove tubes from centrifuge and transfer supernatant to a fresh 10 ml centrifuge tube without disturbing the cellular layer using a disposable serological pipette or disposable bulb pipette. After transferring the plasma to a new 10 ml centrifuge
tube as described, gently mix plasma and record total plasma volume (~8-10 ml plasma per 20 ml blood).

f) Transfer 1 ml plasma aliquots with a pipette to 2 ml pre-labeled cryogenic vials.

g) Place plasma tubes into storage box and freeze plasma in freezer upright in storage box at -70°C or colder. Short time storage at -20°C is possible.

Step #3 - Specimen Storage

a) Sample are maintained continuously at -70°C or colder.

b) When outside the freezer, such as when transferring to a different freezer in another location or preparing for shipment, boxes containing tubes should be covered with dry ice.

c) Freezer or dry ice specimen storage container temperature must be checked and monitored. Document any deviation from protocol.

d) The freezer or dry ice storage box containing the specimens should either be locked or in a secure area accessible only to authorized study staff.

e) A backup storage plan should be in place in the event of freezer failure.

Pharmacokinetic Studies

These studies are being performed to determine if the steady state pharmacokinetics of ipatasertib is altered when administered in combination with the other anticancer agents, by comparison to historical data for single agent ipatasertib, in patients enrolled in dose-escalation portion of Arm C. Pharmacokinetic sampling will be performed in all patients to provide data that may be informative for dose escalation decisions and correlation analysis with clinical and pharmacodynamic data.
The predose samples should ideally be obtained as close as possible to the time that the dose is taken but not more than 60 min before dosing. Patients must be instructed to take the daily dose of ipatasertib in the morning, at the same every day, which should be at a time that will allow the patient to arrive at the clinic to obtain pharmacokinetic samples before dosing and to remain for an additional 8 hours. It is very important that the patient is aware that the morning dose of ipatasertib must not be taken before arriving at the clinic on days when predose pharmacokinetic samples are to be collected. The time that each dose of ipatasertib is taken on all days when pharmacokinetic samples are collected must be accurately recorded. A battery-powered digital timer/stopwatch operated continuously as a 24-h clock should be used to monitor the actual drug administration and sample collection times.

Blood samples are to be collected from a peripheral vein in the arm of the patient in 3 mL plastic purple stoppered Vacutainer tubes with spray dried K$_2$EDTA (Becton Dickinson no. 367856). When using a peripheral catheter for sampling, use a syringe to clear the catheter of the lock solution approximately 1 min before the specified sample time and withdraw about 0.5 mL of blood into the syringe for disposal. Immediately after filling each collection tube, gently invert it 5-times to thoroughly mix the blood with the anticoagulant and place the tube on wet ice until centrifuged. Centrifuge the blood collection tubes within 60 min of collection at 1,500 x g for 10 min at 4°C. Use a disposable pipette to transfer the plasma, removed without disturbing the blood cells, equally into two 2.0 mL self-standing polypropylene cryogenic storage vials with external threads for the primary (aliquot A) and backup (aliquot B) aliquots. Affix a computer printed cryo storage label (e.g., Fisherbrand Micryo Laser Printer Label Sheets for Cryo Storage, item no. 15930E) with the following information onto the tube: Protocol no. 19-086, subject study no., PK Plasma, sample no., aliquot letter, collection date. Orient the label crosswise toward the upper part of the tube being careful not to overlap the vial cap. Immediately place the cryovials in crushed dry ice until transferred to an ultralow temperature freezer (-80 ± 10°C) for storage until shipment.

Ship the complete set of Aliquot A cryovials for each patient within one week after the last sample has been collected. Ship the Aliquot B cryovials separately after verifying receipt of the Aliquot A samples. Do not send the Aliquot A and Aliquot B cryovials for the same patient in the same package. Place the complete set of cryovials for each patient in a fiberboard box sealed within a zip lock plastic bag. Put at least 4 inches of crushed dry ice in a seamless styrofoam container. Place the plastic bag containing the cryovials in the fiberboard box on top of the crushed dry ice and cover it with an additional 4 inches or more of dry ice. Seal the styrofoam container in a tight-fitting cardboard shipping box. Send the samples on Monday to Wednesday by overnight courier for delivery by 10:00 a.m. on the following day to:

Dr. Jeffrey G. Supko  
Massachusetts General Hospital  
55 Fruit St., GRJ 1025  
Boston, MA 02114  
Tel: 617-726-5854

Never ship samples on a Thursday or Friday. Advance notification of an impending shipment and the courier tracking no. of all shipments must be made by email to (1)
MGHCCPOSPL@partners.org; and (2) jsupko@partners.org. Attached a scanned copy of the Pharmacokinetic Time Record for all samples included in the shipment to the email.

Pharmacokinetic samples will be assayed by the DF/HCC Clinical Pharmacology Core laboratory located at the Massachusetts General Hospital (Boston, MA). The concentration of ipatasertib will be determined using an analytical method based upon high performance liquid chromatography with tandem mass spectrometric detection validated as recommended by the current FDA Guidance for Industry: Bioanalytical Method Validation, May 2018. Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Descriptive statistics will be calculated for the pharmacokinetic parameters estimated for the group of patients at each dose level. Mean values of pharmacokinetic parameters will be statistically compared after logarithmic transformation of the data.