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CANADIAN CANCER TRIALS GROUP (CCTG)

A DOUBLE-BLIND PLACEBO CONTROLLED RANDOMIZED PHASE III TRIAL OF FULVESTRANT AND IPATASERTIB AS TREATMENT FOR ADVANCED HER-2 NEGATIVE AND ESTROGEN RECEPTOR POSITIVE (ER+) BREAST CANCER FOLLOWING PROGRESSION ON FIRST LINE CDK 4/6 INHIBITORAND AROMATASE INHIBITOR (FINER)

CCTG Protocol Number: **MA.40**
BCT Protocol Number: **2101**
Roche Protocol Number: **MO41883**

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CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary and must be kept in confidence.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG and Hoffmann-La Roche Ltd. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG and Hoffmann-La Roche Ltd. of any such disclosure.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG or Hoffmann-La Roche Ltd with or without cause.

_____	_____	_____
Qualified Investigator Signature	Printed Name	Date

Protocol Number: CCTG MA.40

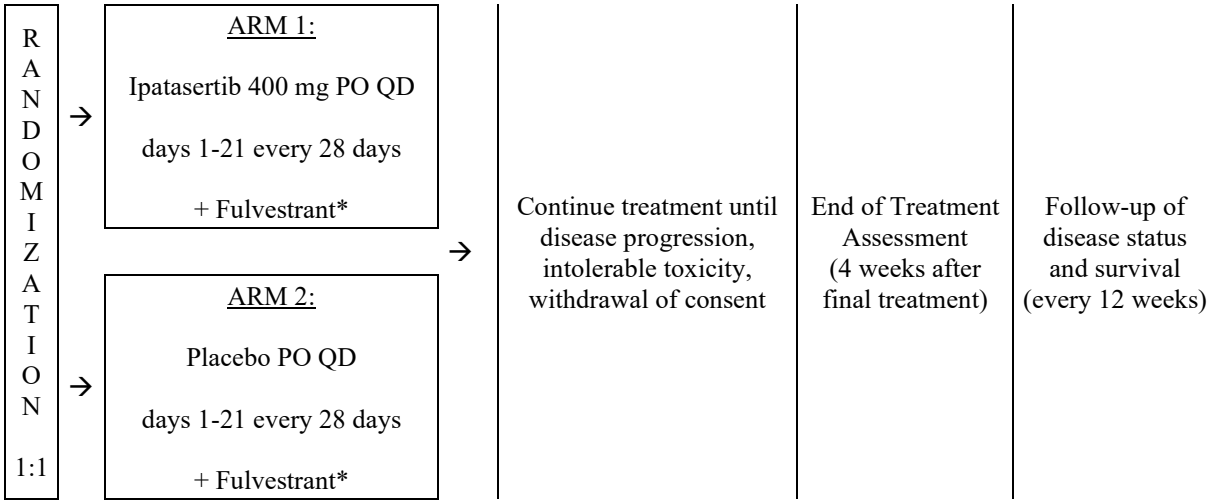
CENTRE: _____

TREATMENT SCHEMA

This is an international multi-centre, double-blind, randomized phase III trial comparing ipatasertib and fulvestrant with placebo and fulvestrant in patients with advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 (HER-2) negative breast cancer after progression on first line CDK 4/6 inhibitor and aromatase inhibitor (AI).

Stratification:

- PIK3CA/PTEN/AKT-1 status: altered versus wildtype/unknown;
- Prior treatment duration with CDK 4/6 inhibitor: < 6 months versus ≥ 6 months.



N = 250 patients

* Fulvestrant 500 mg IM cycle 1 days 1 and 15 followed by 500 mg IM day 1 q 28 days subsequent cycles

1.0 OBJECTIVES

1.1 Primary Objective

To compare investigator assessed progression free survival (PFS) using RECIST 1.1 in patients with ER+/HER2- advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) breast cancer treated with ipatasertib and fulvestrant versus placebo and fulvestrant after progression on first line CDK 4/6 inhibitor plus AI treatment.

1.2 Secondary Objectives

Key Secondary Objective:

- To compare the two treatment arms with respect to investigator assessed PFS (per RECIST 1.1) in the PIK3CA/AKT1/PTEN altered cohort;

Additional Secondary Objectives:

To compare the two treatment arms with respect to:

- Investigator assessed PFS (per RECIST 1.1) in the PIK3CA/AKT1/PTEN non-altered cohort;
- PFS as assessed by blinded central radiology review in all enrolled patients, PIK3CA/AKT1/PTEN altered and non-altered cohorts;
- Response rate (RR) (per RECIST 1.1);
- Duration of Response (DoR);
- Clinical Benefit Rate (CBR);
- Overall survival (OS);
- Time to commencement of subsequent line of systemic therapy or death (TSST);
- Safety and tolerability (CTCAE version 5.0);
- Quality of Life (QOL) as measured using EORTC QLQ-C30 and NCI PRO-CTCAE questionnaires;
- Economic Evaluation, including both healthcare utilization and health utilities, the latter measured using EQ-5D-5L.

1.3 Tertiary Objectives

- To compare the PFS (per RECIST 1.1) between the two treatment arms based on PIK3CA/AKT1/PTEN altered status as determined using archival tissue.
- To identify prognostic and predictive biomarkers/signatures for response and resistance.
- To create a biobank of FFPE and cfDNA for future studies (to be specified).
- To create a biobank of digital anatomical images to identify possible predictive and prognostic biomarkers as part of a radiomics analysis.
- To characterize the pharmacokinetics of ipatasertib (C_{min} and C2-4h) when administered in combination with fulvestrant. PK data may be used for population PK modeling and exposure-response modeling as data allow and will be reported separately.

2.0 BACKGROUND INFORMATION AND RATIONALE

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 2.09 million new cases reported in 2018 *[Bray 2018]* accounting for approximately 7% (~626,679) of all cancer deaths each year.

The most common subtype of breast cancer is hormone receptor-positive (ER+) with no amplification of HER2 (HER2-), accounting for approximately 60%–70% of incident cases. This subtype of breast cancer also accounts for the greatest proportion of deaths related to breast cancer. The backbone of treatment for ER+/HER2- breast cancer (both in early and advanced stage) is endocrine therapy. The multitude of trials comparing one endocrine agent to another in the treatment of ER+/HER2- metastatic breast cancer (MBC) have generally failed to improve either progression free (PFS) or overall survival (OS) *[Matutino 2018]*. In the era of targeted therapies, CDK 4/6 inhibitors (CDK4/6i) added to an endocrine agent have nearly doubled PFS (and extended OS in those with OS results); a result seen consistently across the marketed CDK4/6i (palbociclib, ribociclib and abemaciclib) *[Finn 2016; Hortobagyi 2016; Goetz 2017]*. The median PFS with 1st line CDK4/6i and AI is approximately 24 months and this treatment regimen is recommended in the first line setting for patients with ER/HER2- advanced breast cancer *[NCCN Guidelines 2020]*. Despite the significant improvements in PFS in the 1st line setting with this combination, ER+/HER2- breast cancer will ultimately progress, fuelling an ongoing need/rationale for identification of novel and effective treatments in the second line setting.

The most frequently altered pathway in breast cancer is the PI3K-AKT-mTOR pathway *[Cancer Genome Atlas Network 2012]*. Approximately 45%-50% of ER+ breast cancers display PIK3CA/AKT1/PTEN alterations *[Cancer Genome Atlas Network 2012; Curtis 2012; Pereira 2016]*. PTEN is a tumour suppressor gene involved in multiple important cell functions relating to cell proliferation, survival and genome stability via multiple pathways. Specifically, it acts as a negative regulator of the PI3K/AKT pathway. *[Bazzichetto 2019]*. Upregulation of AKT signalling (whether intrinsic or induced following chemotherapy) represents a potentially important survival pathway in response to genotoxic/mitotic stress. Somatic non-silent mutations in PTEN, PIK3CA and AKT1 are also described. In pre-clinical models, activation of this pathway can lead to ligand independent activation of the estrogen receptor *[Miller 2011]*. Alterations in this pathway have been implicated as a mechanism of resistance to hormonal therapy and potentially also to CDK4/6i–particularly loss of PTEN function *[Herrera-Abreu, 2016]*. In a correlative sub-study of PALOMA-3, cell free DNA (cfDNA) analyses on the end of study treatment samples demonstrated an increased detection rate of PIK3CA mutations (28%) and also demonstrated AKT1 mutations (3.2%) *[O'Leary 2018]*.

Targeting the PI3K-AKT-mTOR pathway

Evidence exists in the clinical setting for targeting the PI3K-AKT-mTOR pathway in ER+/HER2- breast cancer. BOLERO-2, a phase III study with an mTOR inhibitor, led to regulatory approval of everolimus *[Baselga 2012]*. BOLERO-2 compared everolimus plus exemestane vs. placebo plus exemestane in postmenopausal patients with ER+/HER2- MBC who had recurrence or progression after treatment with a nonsteroidal AI in either adjuvant setting or in advanced disease. Median PFS in the everolimus group was 6.9 months, compared with 2.8 months in the placebo group. The hazard ratio (HR) for PFS by investigator assessment was 0.43; p=0.001. Furthermore, in the randomized, double-blind, placebo-controlled, Phase II study PrE0102 *[Kornblum 2018]* in postmenopausal women with ER+/HER2-, AI-resistant MBC, the addition of everolimus to fulvestrant improved the median PFS (mPFS) from 5.1 to 10.3 months (HR=0.61, stratified log-rank p=0.02).

Several PI3K inhibitors have been combined with fulvestrant showing promising activity in Phase III studies in patients with ER+/HER2- MBC who had progressed on or after an AI. In the Phase III BELLE-2 study, buparlisib (a pan-PI3K inhibitor) when combined with fulvestrant resulted in mPFS of 6.9 months versus 5.0 months in the placebo group (HR 0.78; one-sided p=0.00021) in unselected patients *[Baselga 2017]*. In an exploratory analysis of patients with PIK3CA-mutant tumour by circulating tumour DNA (ctDNA), mPFS was 7.0 months in the buparlisib group versus 3.2 months in the placebo group (HR 0.58; one-sided p=0.001).

In the phase III SANDPIPER study, the addition of taselisib (a beta-sparing PI3K inhibitor) to fulvestrant showed a statistically significant improvement in investigator-assessed PFS in patients with PIK3CA-mutant tumours who comprised the primary endpoint population. Median PFS increased from 5.4 months in the placebo arm to 7.4 months in the taselisib arm (HR 0.70, p=0.0037) *[Baselga 2018]*. The study also enrolled a smaller cohort of patients without detectable PIK3CA-mutant tumours for exploratory analyses of PFS. Although the study was not powered to compare the two cohorts, the HR for PFS was similar in patients without detectable PIK3CA-mutant tumours and those with PIK3CA-mutant tumours based on an exploratory analysis. Thus, a treatment effect of taselisib and fulvestrant in patients without detectable PIK3CA mutations could not be completely ruled out.

In the phase III SOLAR-1 study, the addition of alpelisib (an alpha selective PI3K inhibitor) to fulvestrant showed a statistically significant improvement in investigator-assessed PFS in patients with PIK3CA-mutant tumours *[André 2019]*. Median PFS increased from 5.7 months in the placebo arm to 11 months in the alpelisib arm (HR 0.65, p-value = 0.00065) *[André 2019]*. Based on the exploratory analysis, patients without detectable PIK3CA-mutant tumours did not seem to benefit from the addition of alpelisib to fulvestrant.

More pertinent to this protocol was a recently presented randomized placebo-controlled phase II FAKTION trial of an AKT inhibitor, capivasertib (AZD5363) given with fulvestrant upon progression on an AI in ER+ MBC *[Jones 2019]*. This study of 140 patients all received an AI either in the adjuvant setting (11%) or in the metastatic setting (89%); 28% of patients had two or more lines of endocrine therapy for MBC. 26% received one line of chemotherapy for MBC. In the ITT analysis, the PFS was improved from 4.8 to 10.3 months (HR 0.58; p=0.005). Interestingly, the HR for the PI3K/AKT/PTEN-altered tumours (0.59) was similar compared to the HR for the PI3K/AKT/PTEN non-activated tumours (0.56). Thus the benefit appears to be regardless of pathway status as determined by study definition. Grade 3 toxicities were frequent with 14% of patients experiencing grade 3 diarrhea, 20% experiencing grade 3 rash, and 4% experiencing grade 3 hyperglycemia. There were no grade 4/5 events in these categories. Grade 3 infections occurred in 5% of patients and 1% of patients experienced grade 4 infection.

Ipatasertib

Ipatasertib is a potent, highly selective, small-molecule inhibitor of all three isoforms of the serine/threonine kinase AKT. Ipatasertib is being developed by Genentech/Roche as both a single agent and in combination with other therapies for the treatment of cancers in which activation of the PI3K-AKT-mTOR pathway may be relevant for tumour growth or therapeutic resistance.

In pre-clinical models with high levels of phosphorylated AKT or PI3K-AKT-mTOR pathway activity (i.e. PIK3CA mutation, PTEN alterations), sensitivity to ipatasertib has been observed across different tumour models, including breast cancers *[Lin 2013]*. In vivo efficacy studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumours *[Lin 2013]*. Clinical studies in a variety of tumour types have been conducted with ipatasertib both as monotherapy and in combination *[Saura 2017]*. Combination partners have included hormonal therapies (i.e. abiraterone and enzalutamide), chemotherapy, and immunotherapy. Randomized studies with ipatasertib have been conducted in breast, prostate, and gastric cancer.

Combination with Fulvestrant

At present the standard of care for the majority of patients newly diagnosed with ER+/HER2- MBC is first line treatment with a CDK 4/6 inhibitor in combination with an AI. The optimal second line of therapy remains unclear. Current guidelines recommend fulvestrant as a treatment option for receptor positive breast cancer in the advanced/metastatic setting, including in combination with targeted PI3K inhibitor therapy *[NCCN Guidelines 2020]*.

Quality of Life (QOL)

Given the incurable nature of advanced breast cancer and the incidence of treatment related adverse events associated with therapy, patient reported outcomes (PRO) data provide an important perspective on the impact of an intervention, above and beyond treatment induced changes in lifespan. Increasingly, values of new drugs are evaluated with framework combining benefit (e.g. survival, progression-free survival), toxicities and cost. ASCO and ESMO have created scales to capture these elements including QOL *[Cherny 2017; Schnipper 2015]*. These scales allow comparisons of benefits of different treatment and their cost.

In the current protocol, we will evaluate the addition of an oral targeted therapy to an endocrine treatment, the last one having relatively few side effects. Available toxicity data about ipatasertib showed toxicities that can impact QOL such as diarrhea and rash. Therefore, once the trial is completed, if positive, we will need to weigh the added benefit, against the added toxicity and impact on overall quality of life. In other trials examining the addition of a targeted therapy to a backbone of endocrine therapy, QOL data have been helpful to inform clinicians and patients that even if the combination treatment has more side effects, overall there was no detrimental effect on QOL *[Rugo 2018; Harbeck 2016; Verma 2018; Kaufman 2019; Campone 2013]*.

We know from the FAKTION study (fulvestrant plus capivasertib or placebo) and from the LOTUS study (paclitaxel plus ipatasertib or placebo) that diarrhea is the most commonly reported adverse event experienced with AKT inhibitors, with any grade of diarrhea being reported in 81% and 92% of patients respectively. It is also known that this symptom is usually underreported by patients, and the impact of diarrhea on overall quality of life can be missed *[Atkinson 2012; Lui 2017]*. In the recent published PAKT trial *[Schmid 2020]* using capivasertib or placebo with paclitaxel, there was a statistically significant increase in the capivasertib arm of diarrhea, skin dryness, rash and fatigue.

The objectives of the quality of life components of this study are to compare patients' overall quality of life between the two treatment arms with specific analyses related to the symptoms of diarrhea, rash, fatigue and pain as described below.

Two instruments will be used to capture the QOL experience of patients: the EORTC QLQ-C30 and the PRO-CTCAE. The EORTC QLQ-C30 will be used to capture the multidimensionality of QOL in metastatic breast cancer. The EORTC QLQ-C30 is a widely used, cancer specific health-related QOL questionnaire which is well accepted by patients *[Aaronson 1993; Conroy 2004]*. It contains five functional subscales (physical, role, cognitive, emotional, social), three multi-item symptom subscales (fatigue, pain and nausea), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact) and a global health measure (physical condition and global QOL). The questionnaire uses 4 and 7-point scales. For each subscale, the range of possible scores is between 0 and 100. Convergent and criterion validity has been demonstrated for this questionnaire in metastatic breast cancer *[Bottomlay 2004; Mclachlan 1998]* and reliability is adequate *[Aaronson 1993; Hjermstad 1995]*. The EORTC QLQ-C30 has been shown to be responsive to change associated with chemotherapy and with disease progression *[Osoba 1998; Lemieux 2007]*. The questionnaire is available in multiple languages.

Given important toxicities/symptoms in this population (eg. diarrhea, rash, fatigue and pain), we will complement the EORTC QLQ-C30 with the PRO-CTCAE. Although these symptoms (except skin problems) are measured in the EORTC QLQ-C30, they are measured using a 5-point Likert scale with PRO-CTCAE (compared to a 4-point in the EORTC QLQ-C30) and also look at the frequency, severity and interference of symptoms. PRO-CTCAE is a validated tool designed by the National Cancer Institute by multidisciplinary investigators and patients, which provides a patient-centred approach to adverse event assessment in clinical research *[Basch 2014]*. Its content has been evaluated for validity through a cognitive interviewing study, and its construct validity, reliability and responsiveness were examined in a US multicenter study *[Hay 2014]*. This tool was designed to complement the CTCAE and can be utilized in phase III clinical trials to assess adverse reactions and provide data comparing tolerability between regimens. It is available in multiple languages. Selected items of the PRO-CTCAE for diarrhea, skin toxicities, pain and fatigue will be used. To date, there are no standardization as what is a minimally clinically important difference.

The two questionnaires will be administered at baseline, at day 1 of cycles 2-4 and then every 2 cycles (corresponding with the timing of imaging for disease assessments), 4 weeks after discontinuation of study medication and at 3 months follow up (only required for patients without confirmed progressive disease and/or with ongoing toxicities). Given this trial has a small sample size, we will collect data on all patients enrolled in this study.

Economic Evaluation

Determining health care value is critical to the adoption of new technologies and procedures in the health system and society. The health economic evaluation of this study will evaluate the cost-effectiveness and cost-utility of ipatasertib and fulvestrant combination therapy in comparison with fulvestrant alone. If the addition of ipatasertib is found to produce a clinical benefit as a second-line treatment for metastatic ER+ breast cancer, the economic evaluation will assist decision-makers in defining the cost-benefit trade-offs of adding this drug to their formulary. Collecting cost, productivity, and utilization data will also facilitate a robust estimate of the value of fulvestrant. The primary model outcomes of this model will be the cost per additional year of progression-free survival (PFS) and overall survival (OS), the cost per additional quality-adjusted life year (QALY) gained, and a budget impact analysis.

We will conduct the analysis from the perspective of the public healthcare payer. Direct health care costs will be based on the cost of treatment at a tertiary cancer centre in current Canadian dollars. It is assumed that the Ontario provincial perspective could be considered representative of the Canadian public healthcare system; therefore, costs will be derived using local estimates and Ontario Health Insurance Plan (OHIP) billing codes. Costs of outpatient medications will be determined with the Ontario Drug Benefit Formulary plus an 8% markup fee as permitted by the Ontario government. Non-formulary medications will include a 15% markup, reflecting current outpatient pharmacy practice. Costs of outpatient visits will be determined using the hotel approximation method, which includes all overhead and staffing costs.

Utilization data will be collected prospectively from all patients on the trial. A mean treatment cost per patient in each arm of the study (Arm 1: ipatasertib + fulvestrant; Arm 2: placebo + fulvestrant) will be generated based on the following utilization data:

1. Drug Costs:
    a. Cost of ipatasertib, fulvestrant, and any supportive medication used during the study.
    b. Costs related to administration and outpatient assessment.

2. Costs of managing adverse events:
    a. Investigations.
    b. Emergency department visits.
    c. Additional physician visits (primary care, specialist care).
    d. Inpatient admissions (duration, most responsible diagnosis).

3. Cost of subsequent cancer therapy at time of relapse:
    a. Outpatient assessment.
    b. Chemotherapy and radiotherapy administration, surgical intervention as appropriate.
    c. Hospitalization and supportive care.

The EQ-5D-5L will be administered to all participants to generate a utility (with values from 0 to 1) to quality-adjust the clinical outcomes. The EQ-5D-5L consists of 5 dimensions, including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression and respondents use 3-level response categories to indicate the level most descriptive of their current level of function on each dimension. Five dimensions, each with three levels, yield 243 possible distinct health states comprising the classification system, which can then be used to generate a utility (with values from 0 to 1). Mean utility values for the two study arms will be estimated.

The EQ-5D-5L will be administered at the following intervals: baseline (pre-risk notification at time 0), after every second cycle, and 3 months after protocol completion. The EQ-5D-5L will be additionally administered at 24 months after enrollment and annually thereafter until the time of second treatment, death, removal from study, or completion of 5 years of follow-up.

Correlative Studies

Tissue and Fluid Based Correlative Studies

Correlative studies are a key component of this clinical trial. Randomization to treatment arms will be stratified by PIK3CA/PTEN/AKT-1 alteration status derived from cfDNA analysis and secondary endpoints will be calculated for each strata to determine if this pathway alteration impacts ipatasertib activity.

The planned cfDNA and tissue based assays are intended to capture quantifiable genomic, epigenomic and proteomic longitudinal alterations. When integrated with response data, this will facilitate the development of prognostic and predictive biomarkers related to ipatasertib sensitivity.

Assays will be repeated at regular intervals while patients are on study to explore genomic changes associated with response, progression and resistance to fulvestrant and ipatasertib. The correlative samples collected will allow for comparison of differential genomic and proteomic changes between the two study arms.

Additionally, an evaluation of blood-derived exosomes is planned. Exosomes are small vesicular particles produced by viable cells that have recently been implicated in key cellular processes including paracrine and autocrine cell signalling. A variety of cellular molecules are packaged within exosomes including proteins, lipids, messenger RNAs, microRNAs, and DNA. It is believed that cancer cells release an increased number of exosomes as compared to normal cells; thus the exosomal contents represent potential biomarkers that may be related to patient prognosis or response to therapy.

A tertiary endpoint of this study is to build a bank of blood and tissue samples for future exploratory investigations. Details of correlative study requirements can be found in section 12.0 of the protocol.

Image Based Correlative Studies (Radiomics)

Radiomics refers to processes of automated computational extraction and analysis of quantitative information derived from anatomic/functional imaging of tumours and surrounding tissue with a goal of deriving information related to response to treatment and disease outcomes *[Nie, 2019]*. Advantages of radiomics compared to tumour tissue analysis relate to the avoidance of invasive procedures and potentially a better assessment of tumour heterogeneity, a recognized phenomenon in metastatic breast cancer *[Lindstrom 2012; Roulot 2016]*.

Currently, radiomics research is mainly exploratory with respect to biological and analytical validity *[Hayes 2014, Tagliafico 2020]*. Integration of radiomic research into clinical trials thus offers an important opportunity to collect and analyze imaging data using a recognized framework that is based on biomarker collection, storage and analysis of biological tissue *[McShane 2013]*.

Ultimately, research from this trial and others will further the goal of adding radiomics information to the personalized medicine paradigm that currently includes host, epidemiological and biological tissue derived information to individualize anticancer treatment plans.

A tertiary endpoint of this study is to build an anatomical image bank for future exploratory investigations. Details of correlative study requirements can be found in section 12.0 of the protocol.

Summary

This international, randomized, placebo-controlled phase III trial of fulvestrant with ipatasertib/placebo will examine the existing gap in breast cancer knowledge and treatment in the second line setting for ER+/HER2- patients after progression on CDK4/6i and AI therapy. Correlative work will examine the impact of pathway alterations on prognosis and response to therapy.

The current proposal entails a comprehensive examination of the impact of treatment with fulvestrant and ipatasertib/placebo via the collection of efficacy, quality of life, economic, safety and adverse event data.

3.0 BACKGROUND THERAPEUTIC INFORMATION

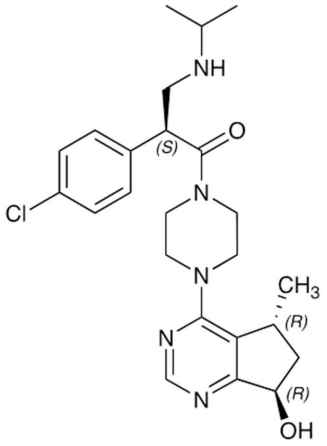
3.1 Ipatasertib

Please see the current ipatasertib Investigator Brochure for the most up to date information.

3.1.1 *Name and Chemical Information (Ipatasertib)*

(S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

3.1.2 *Chemical Structure*



3.1.3 *Mechanism of Action*

Ipatasertib is a potent and selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase AKT and is being developed by Genentech/Roche as a single agent and in combination with other therapies for the treatment of cancers in which activation of the PI3K-AKT-mTOR pathway may be relevant for tumour growth or therapeutic resistance. Ipatasertib selectively binds to the active conformation of AKT and inhibits its kinase activity *[Lin 2012]*. Ipatasertib has proven to be especially effective on cells with activated AKT, including PTEN-null and PI3K-mutated tumour models, leading to suppression of the phosphorylation of its direct substrates. Consistent with the role of AKT in insulin signalling, ipatasertib also exhibited dose-dependent and reversible elevation of serum glucose in pre-clinical studies. In vivo studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumours *[Lin 2013]*.

3.1.4 *Experimental Anti-tumour Activity*

In vivo efficacy of ipatasertib was established using various in vivo mouse xenograft models, in which the PI3K-AKT-mTOR pathway is aberrantly activated as a result of PI3Kα mutation or decreased PTEN expression. Anti-tumour activity was evaluated, shown as percentage of tumour growth inhibition (TGI) relative to vehicle controls for ipatasertib as a single agent or in combination with either chemotherapeutics or targeted agents (e.g. docetaxel, paclitaxel, mFOLFOX6, abiraterone, and MDV3100). These in vivo studies demonstrated that ipatasertib has robust anti-tumour activity as a single agent and improved efficacy when administered in combination with other marketed or experimental cancer agents.

In the phase Ib study PAM4983g, 2 of 5 patients with ER+/HER2- breast cancer who were treated with the combination of ipatasertib and paclitaxel, had confirmed partial responses. The randomized phase Ib/II study GO27983 was conducted in patients with metastatic castration resistant prostate cancer (mCRPC) post-docetaxel. When added to hormonal therapy abiraterone plus prednisone/prednisolone, ipatasertib (400 mg) showed improved PFS compared with abiraterone and prednisone/prednisolone in the all-comer population and in patients with PTEN-loss tumours (HR 0.75 in all-comers; HR 0.39 in PTEN-loss by immunohistochemistry [IHC] assay) *[de Bono, 2019]*. There is an ongoing randomized Phase III study CO39303 evaluating ipatasertib 400 mg when added to abiraterone and prednisone/prednisolone compared to abiraterone and prednisone/prednisolone in front-line mCRPC.

The randomized phase II study, GO29227, evaluated the addition of ipatasertib to paclitaxel in front-line metastatic triple-negative breast cancer (TNBC) patients and those with a PTEN loss (by IHC) and separately, patients with PIK3CA/AKT1/PTEN-altered tumours *[Dent 2018]*. Results from this study showed improvement in mPFS in the intent-to-treat (ITT) population of 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm (stratified HR 0.60; p=0.037) with even greater improvement in PIK3CA/AKT1/PTEN-altered tumours of 9 months vs. 4.9 months (non-stratified HR 0.44; log-rank p=0.041). There is an ongoing randomized phase III study CO40016 evaluating 400mg ipatasertib when added to paclitaxel compared to paclitaxel for patients with PIK3CA/AKT1/PTEN altered tumours in both first-line TNBC and HR+/HER2- breast cancer with no prior chemotherapy.

3.1.5 *Animal Toxicology*

Ipatasertib was not mutagenic or clastogenic when evaluated in a standard ICH genotoxicity battery, was not phototoxic in-vitro, and did not demonstrate adverse effects on cardiovascular and respiratory function in monkeys or on neurological system function in rats. Daily oral dosing of ipatasertib for up to 26 weeks was well tolerated at doses up to 2 mg/kg in rats and 15 mg/kg in monkeys. The toxicity profile of ipatasertib was generally consistent in the 4, 13, and 26 week studies; no new adverse findings or evidence of progression of previously identified toxicities were identified in the 26-week studies.

The most prominent findings in rats and monkeys administered ipatasertib were pharmacologically-mediated, acute hyperglycemia and increased serum insulin concentration, and compensatory hypertrophy and hyperplasia of pancreatic islet cells and hepatocellular glycogen accumulation in the liver. These effects were observed at subclinical exposures (AUC0–24) of approximately 0.02-fold that in patients receiving 400 mg/day, and are indicative of PD activity based on the key role of AKT in signal transduction downstream of the insulin/insulin growth factor receptor *[Whiteman 2002]*. The dose-dependent increases in glucose and insulin resolved rapidly after discontinuation of dosing, while hepatic and pancreatic changes demonstrated evidence of reversibility during the recovery period. Of note, for the 26-week studies, the pancreatic islet and hepatic findings in the rat were similar to the 13-week study, but in the monkey, the hyperglycemic response was not maintained for the full dosing period, nor were there histologic correlates. There was no evidence of adverse effects on male or female reproductive organs in monkeys or rats given ipatasertib for up to 26-weeks or male reproductive assessment parameters (i.e. sperm count, morphology, and motility) in the 13-week repeat-dose studies, but the potential for ipatasertib-mediated embryo-fetal toxicity was identified in rat and rabbit embryo-fetal development studies. Other clinical pathology changes that were observed in both species included decreased circulating reticulocyte and lymphocyte counts and increased total serum cholesterol concentration. The mild, reversible elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum levels and hepatocellular vacuolation observed at the high dose in the 4-week study in rats (not observed in the 13- or 26-week studies) occurred at exposures approximately 3-fold the AUC24h,ssexposure (4450ng•hr/mL) in patients administered 600mg QD.

3.1.6 *Phase I Trials*

Study PAM4743g was an open-label, phase I, dose-escalation study that used a 3 + 3 design to assess the safety, tolerability, and PK profile of oral ipatasertib administered daily to patients with refractory solid tumours. A total of 52 patients were enrolled in this study; 51 patients received treatment with ipatasertib.

Study PAM4743g is complete. The MTD was exceeded at 800 mg daily on a 21/7-dosing schedule, with DLTs of grade 3 asthenia (n = 1) and grade 3 nausea (n = 1). The MTD of ipatasertib is 600 mg daily for 21 days followed by 7 days off-dosing schedule. The recommended phase II dose was 400mg daily for 21 days on a 4 week schedule.

The combination of ipatasertib and fulvestrant +/- palbociclib is currently being investigated in the phase Ib setting with the TAKTIC (NCT03959891) and CO41012 (NCT04060862) studies.

3.1.7 *Phase II Trials*

Study GO29227 is a multi-center, phase II, global study to estimate the tolerability and clinical activity of ipatasertib 400 mg in combination with paclitaxel versus placebo in combination with paclitaxel in patients with locally advanced or metastatic TNBC, as measured by PFS, OS, ORR, and duration of confirmed response in all patients and in patients with tumours that have low PTEN expression. A total of 63 patients received treatment with ipatasertib.

145 patients have received ipatasertib in combination with paclitaxel in the HR+, HER2- cohort of the phase III IPATunity130 (NCT0333772) study.

3.1.8 *Pharmacokinetic Studies*

The PK of ipatasertib and its major metabolite, G-037720, was assessed in patients with cancer in the phase I study PAM4743g. Ipatasertib showed rapid absorption, with median t_{max} ranging from 0.5 to 3.0 hours across all doses. In general, the exposure of ipatasertib was dose-proportional from 200 to 800 mg. The mean terminal half-life ranged from 31.9 to 53 hours at doses of 100 mg and above. Steady-state exposures were achieved following 8 days daily oral dosing.

In vitro metabolism data indicate that ipatasertib is a time-dependent inhibitor of CYP3A. Therefore, sensitive substrates of CYP3A with a narrow therapeutic index should be avoided or administered with caution. Given the mean change of 2.22-fold, ipatasertib would be classified as a mild-moderate CYP3A inhibitor at doses of 400-600 mg, and is not expected to cause clinically significant DDIs for those CYP3A substrates that do not have a narrow therapeutic index.

Ipatasertib is primarily metabolized by CYP3A4 (refer to ipatasertib Investigator's Brochure), and itraconazole, a strong CYP3A4 inhibitor, increased ipatasertib area under the concentration-time curve (AUC) and maximum concentration (C_{max}) by approximately 5-fold and 2-fold, respectively as observed in Study GP30057.

Co-administration of 400 mg or 600 mg ipatasertib with 160 mg enzalutamide, a strong CYP3A4 inducer, decreased the steady state C_{max} and AUC of ipatasertib by approximately 50% as observed in the PAM4983g study.

Based on two relative bioavailability studies, exposure to ipatasertib following phase II or phase III formulation film-coated tablets is expected to be comparable and food is not expected to impact level of exposure to the drug.

Although fulvestrant is a CYP3A4 substrate, strong CYP3A inhibitors and inducers did not have clinically relevant effect on fulvestrant disposition (Faslodex® package insert). Based on this, although ipatasertib is a mild-to-moderate inhibitor of CYP3A4 (Study PAM4743g; see the Ipatasertib Investigator's Brochure for details), ipatasertib is not expected to alter the exposure of fulvestrant in a clinical meaningful way. Fulvestrant is not an inhibitor or inducer of CYP3A (Faslodex® package insert), and therefore, it is not expected to alter plasma exposure of ipatasertib.

3.1.9 *Justification of Dose Selection*

The dose and schedule of ipatasertib (400 mg QD, days 1-21 of each 28 day cycle) is based on the RP2D identified in studies PAM4743g (phase I), PAM4983g Arm C (Phase Ib) and GO27983 (phase Ib/II).

3.1.10 *Pharmaceutical Data*

Supplied:

The phase III formulation film-coated tablets 100 mg and 200 mg are differentiated by size, colour, and weight of the tablets. The ingredients in the tablets include microcrystalline cellulose, pre-gelatinized maize starch, croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate (non-bovine), and Opadry®II Yellow film coat (100 mg tablet) or Opadry II Pink film coat (200 mg tablet).

The ipatasertib phase III placebo tablets have been manufactured to match the size, shape, and colour of the ipatasertib active tablets (100 mg and 200 mg) and are indistinguishable in appearance from the ipatasertib active tablets. The ingredients in the phase III placebo tablets include microcrystalline cellulose, mannitol, magnesium stearate (non-bovine), and Opadry®II Yellow film coat (placebo for 100 mg tablet) or Opadry II Pink film coat (placebo for 200 mg tablet).

All excipients used in the phase III active and placebo tablet formulations are compendial grade, with the exception of the film coatings. The ingredients in the film coatings are compendial.

Storage:

Ipatasertib active and placebo tablets are packaged in high-density polyethylene bottles with desiccant. The storage condition is "Do not store above 25°C, protect from moisture." Information on storage conditions and shelf life of the active and placebo tablets is provided on the label.

Route of Administration:

Oral (PO).

3.2 Fulvestrant

Fulvestrant is an approved endocrine therapy for advanced ER+ breast cancer. Please see the current fulvestrant Product Monograph for the most up to date information.

Ovarian suppression therapy (LHRH agonists, surgical or radiologic ovarian ablation) is required for all pre-menopausal women receiving fulvestrant who have not had a bilateral oophorectomy. LHRH agonists will not be supplied or reimbursed.

3.2.1 *Mechanism of Action*

Fulvestrant is an estrogen receptor (ER) antagonist that has a mode of action leading to downregulation of ER protein. Fulvestrant is a nonagonist ER antagonist that blocks the trophic actions of estrogens without itself having any partial agonist (estrogen-like) activity. Fulvestrant binds to estrogen receptors in a competitive manner with an affinity comparable to that of estradiol.

3.2.2 *Pharmaceutical Data*

Supplied:
Fulvestrant solution for injection is a clear, colourless to yellow, viscous liquid provided in a package of two pre-filled 250 mg/5mL (50 mg/mL) syringes. In addition to the active ingredient fulvestrant, each syringe also contains the following non-active ingredients: ethanol 96%, benzyl alcohol, benzyl benzoate and castor oil.

Storage:
Store refrigerated at 2 to 8°C. Store in original package and do not break the seal, in order to protect it from light. Packages are single use only and any unused portion must be discarded.

Route of Administration:
Fulvestrant 500 mg is to be administered intramuscularly as two 5 mL (250 mg/5 mL) injections (one in each buttock), on day 1 of each cycle as well as on day 15 of cycle 1.

4.0 STUDY POPULATION

This study will include patients with advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) ER+ and HER-2 negative breast cancer who have progressed on first-line CDK 4/6 inhibitor and aromatase inhibitor.

This study has two steps:

1. Screening (registration to assess stratification parameters prior to enrollment);
2. Enrollment to a treatment arm.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar disease(s).

These eligibility criteria are expected to be followed. Any proposed variance must be discussed with CCTG prior to patient enrollment.

Note: Prior to registration, sites must ensure that patients meet all criteria listed below in sections 4.1 and 4.2.

4.1 Eligibility Criteria

4.1.1 Patients must have histologically and/or cytologically confirmed ER positive and HER-2 negative breast cancer by local assessment that is advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) and for which no curative therapy exists. Note: Pathology reports from all prior procedures must indicate ER positive and HER-2 negative if this testing was performed. Please contact CCTG prior to patient registration if previous results do not meet this criteria or are equivocal.

ER positive is defined as ≥ 1% of tumour nuclei positive for ER via IHC analysis. *[CAP Guidelines 2020]*.

HER-2 negative is defined as a negative ISH test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative ISH result is also required. *[CAP Guidelines 2018]*.

4.1.2 Female patients must be post-menopausal as defined by meeting one of the following criteria *[NCCN Guidelines 2020]*:

a. Prior bilateral oophorectomy.

b. Age ≥ 60 years.

c. Age < 60 years and amenorrhoeic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range.

d. If taking tamoxifen or toremifene and age < 60 years, then FSH and plasma estradiol level in post-menopausal ranges.

Female patients who are pre-menopausal must have ovarian suppression using LHRH agonist while on study and for at least 28 days prior to registration with estradiol level assessed within 7 days prior to registration within the local post-menopausal normal range.

4.1.3 Patients must have evidence of clinical and/or radiographic progression during treatment with or within 28 days after discontinuation of first line of treatment with a CDK 4/6 inhibitor and an AI for advanced/metastatic disease, as judged by the investigator.

4.1.4 Presence of clinically and/or radiologically documented disease at the time of registration. Patients must have evaluable disease (as per RECIST 1.1), however, measurable disease is not mandatory. Baseline radiology studies must be performed within 28 days prior to enrollment in order to accurately assess baseline disease burden.

4.1.5 Patients must be ≥ 18 years of age.

4.1.6 Patients must have an ECOG performance status of 0 or 1.

4.1.7 Patients must not be receiving any concurrent anti-cancer therapy and must satisfy the following criteria for previous therapy:

a. Must not have received more than one prior line of treatment with a CDK 4/6 inhibitor and an AI in the advanced disease setting. Treatment with CDK 4/6 inhibitor and AI must have been the most recent treatment prior to registration for this study and treatment with both agents must be discontinued by the date of registration.

b. Must not have received more than one prior line of chemotherapy in the advanced setting. Chemotherapy must have been given prior to first line treatment with CDK 4/6 inhibitor and AI.

c. Patients must have recovered to grade ≤ 1 from all reversible toxicity related to prior anti-cancer systemic therapy. Patients with fatigue ≤ grade 2 related to prior therapy are permitted to enroll.

d. Prior external beam radiation is permitted provided a minimum of 28 days have elapsed between the last dose of radiation and date of enrollment. Exceptions may be made for low-dose, non-myelosuppressive radiotherapy after consultation with CCTG. Concurrent radiotherapy is not permitted.

e. Prior surgery is permitted provided that a minimum of 28 days have elapsed between any major surgery and date of registration for screening and that wound healing has occurred.

4.1.8 Adequate hematology and organ function, in the absence of growth factors, as defined below (must be done within 7 days prior to registration for screening).

Hematology	Absolute neutrophils	> 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	> 90 g/L
Chemistry	Total Bilirubin	≤ 1.5 x ULN (upper limit of normal) or ≤ 3 x ULN if confirmed Gilbert's
	ALT and AST	≤ 2.5 x ULN (or ≤ 5.0 x ULN if liver or bone metastasis)
	Alkaline phosphatase	≤ 2.0 x ULN (or ≤ 5.0 x ULN if liver metastases, ≤ 7.0 x ULN if bone metastasis)
	Fasting glucose	≤ 8.3 mmol/L
	HbA1c	≤ 7.5%
	Serum albumin	≥ 30 g/L
	INR	≤ 1.2
	Serum Creatinine *or* Creatinine clearance	≤ 1.5 x ULN *or* ≥ 50 mL/min; measured directly by 24 hour urine sampling or as calculated by Crockcroft and Gault equation: Females: $GFR = \frac{1.04 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum Cr in } \mu\text{mol/L}}$ Males: $GFR = \frac{1.23 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum Cr in } \mu\text{mol/L}}$

4.1.9 Patients must consent to blood collection at the time of registration for stratification and at subsequent time points for correlative and pharmacokinetic studies. The stratification blood sample cannot be sent for analysis prior to patient registration for screening.

4.1.10 Patients must consent to the submission of, and investigator must confirm access to and agree to submit within 4 weeks of enrollment, a formalin-fixed, paraffin-embedded tumour (FFPE) tissue block, cores (two 2 mm cores of tumour from the block), or a minimum of 20 freshly cut unstained, serial tumour slides from the most recently collected tumour tissue for molecular analysis and for other protocol-mandated secondary and exploratory assessments.

Where no previously resected or biopsied tumour tissue exists or if the tissue is determined to be of inadequate amount or quality, an additional biopsy of the metastatic or primary tumour will be required for the patient to be considered eligible for the study. Please refer to the MA.40 Correlatives Manual for details concerning adequacy of amount and quality of tumour tissue.

4.1.11 Patients must consent to the submission of digital radiology images at the required time points for radiomic analysis and central radiology review.

4.1.12 Female patients of childbearing potential must agree to use two effective contraceptive methods while on study and for 2 years after the last dose of study drug. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months.

Male patients of childbearing potential must have agreed to use a highly effective contraceptive method while on study and for 2 years after the last dose of study drug. Men should not father a child or donate sperm during this period.

Examples of effective methods of contraception are male condom plus spermicide, cap plus spermicide, diaphragm plus spermicide, intrauterine device (Copper T). In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as complete hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he or she is responsible for beginning contraceptive measures.

4.1.13 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life and health utility questionnaires in either English or French. The baseline assessment must be completed within 7 days prior to enrollment. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

4.1.14 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to registration for screening to the trial to document their willingness to participate.

4.1.15 Patients must be accessible for treatment and follow-up. Patients enrolled on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. The patient's city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

Patients must agree to return to the participating centre for response assessment as well as any adverse events which may occur through the course of the trial.

4.1.16 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient enrollment.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen. When a biopsy has been performed of a metastatic lesion(s) and the pathology is supportive of an ER+/HER2- metastatic breast cancer, patients with a prior history of other malignancies are eligible as long as all other eligibility criteria are met. Please consult with CCTG in these cases prior to enrollment.

4.2.2 Patients with untreated or symptomatic CNS metastases or who have had radiation treatment for CNS metastases within 28 days of registration for screening are not eligible. Stable, treated brain metastases are permitted (defined as patients who are off steroids and anticonvulsants and are stable for at least 30 days at the time of registration for screening). Patients with known leptomeningeal disease (LMD) are not permitted to enrol. If the possibility of LMD has been reported radiographically on baseline CT/MRI but is not suspected clinically by the investigator, the patient must be free of neurological symptoms of LMD.

4.2.3 Patients with any of the following gastrointestinal (GI) conditions:

- history of or active inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis);
- active bowel inflammation (e.g. diverticulitis);
- inability to swallow oral medication;
- impairment of GI function or GI disease that may significantly alter the absorption of the oral study drug (e.g. uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

4.2.4 Patients who have received prior treatment with fulvestrant, selective estrogen receptor degraders (SERDs) or known inhibitors of the PI3K pathway including PI3K inhibitors, AKT inhibitors, or mTOR inhibitors.

4.2.5 Patients who have received or are currently receiving treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to registration for screening.

4.2.6 Patients with a mean QT interval corrected for heart rate (QTc) $\geq$ 480 msec by ECG measured using standard institutional method or history of familial long QT syndrome.

4.2.7 Patients with active or uncontrolled infections or with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol. This includes but is not limited to:

- active infection requiring systemic therapy;
- active or known human immunodeficiency virus (HIV) with detectable viral load;
- symptomatic cardiac dysfunction, uncontrolled or recent clinically significant cardiac disease including:
  - unstable angina, symptomatic pericarditis, coronary artery bypass grafting, coronary antioplasty or stenting, or myocardial infarction in the previous 12 months;
  - history of documented congestive heart failure (New York Heart Association functional classification III-IV) or cardiomyopathy;
  - history of 2nd or 3rd degree cardiac ventricular arrhythmias or cardiac ventricular arrhythmias requiring medication;
  - patients with uncontrolled hypertension;
- patients with clinically significant liver diseases consistent with Child-Pugh Class B or C, including viral/other hepatitis, current alcohol abuse or cirrhosis;
- history of lung disease including pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia).

4.2.8 Patients with Type 1 or Type 2 diabetes mellitus requiring insulin. Diabetic patients requiring only oral medication are eligible provided they are on a stable dose of oral medication ≥ 2 weeks prior to registration. Patients must meet the laboratory eligibility criteria for fasting blood glucose and glycated hemoglobin (see 4.1.8).

4.2.9 Patients with grade ≥ 2 uncontrolled hypercholesterolemia or hypertriglyceridemia.

4.2.10 Patients with known abnormalities in coagulation, such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant.

4.2.11 Patients with symptomatic disease burden which precludes full participation in the study interventions and follow up requirements, as judged by the investigator.

4.2.12 Patients with a history of hypersensitivity to the study drugs or components.

4.2.13 Pregnant or lactating women. Women of childbearing potential must have a pregnancy test (urine or serum) proven negative within 3 days prior to enrollment. If urine test is positive, pregnancy testing may then include a serum test and an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient may be considered eligible if a serum test and ultrasound are negative for pregnancy, with approval from CCTG.

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

Required Investigations	Screening (within 7 days prior to registration)	Baseline	During Protocol Treatment (1 cycle = 28 days)	At disease progression	24 months after enrollment	After Protocol Treatment	
						4 weeks after discontinuation of protocol therapy[1]	Every 12 weeks[2]
History and Physical Exam							
Height (baseline only), weight, ECOG performance status	X		Day 1 of each cycle[3]			X	
Concomitant medications	To assess patient for eligibility	X (within 14 days prior to enrollment)	Continuous running log				
Laboratory Assessments[3]							
Hemoglobin, platelets, WBC, neutrophils	X		Day 1 of each cycle[3]			X	X[4]
Serum creatinine or creatinine clearance, sodium, potassium, bicarbonate, magnesium, calcium, phosphate, urea (or BUN), total bilirubin, ALT, AST, ALP, LDH, albumin glucose (fasting)[5]	X		Day 1 of each cycle[3] and day 15 of cycle 1			X	X[4]
Home glucose monitoring[8]			As clinically indicated to manage AEs			As clinically indicated to manage AEs	
HbA1c, cholesterol (fasting), triglycerides (fasting), HDL, LDL, amylase, lipase[6]	X		Day 1 cycle 2 then day 1 of every third cycle.			X	X[4]
INR	X						
Estradiol *(only for pre-menopausal patients on LHRH analog)*	X						
Disease Assessment							
CT/MRI chest, abdomen and pelvis		Within 28 days prior to enrollment	Every 8 weeks for the first 18 months then every 12 weeks until PD[2]			X[2] (if applicable based on timing)	X[2] (disease assessments required as per during protocol treatment schedule until PD)
CT/MRI brain *(only required if known brain metastases or otherwise clinically indicated)*							
Clinical tumour measurements *(if applicable)*							
Whole Body Bone Scan			Every 8 weeks for the first 18 months then every 12 weeks until PD if bone lesions are present at baseline and cannot be assessed by chest / abdomen / pelvis imaging[2]				

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Required Investigations	Screening (within 7 days prior to registration)	Baseline	During Protocol Treatment (1 cycle = 28 days)	At disease progression	24 months after enrollment	After Protocol Treatment	
						4 weeks after discontinuation of protocol therapy[1]	Every 12 weeks[2]
Other Investigations							
Pregnancy Test *(pre-menopausal patients only)*[7]		Within 3 days prior to enrollment	As clinically indicated				
ECG	X		As clinically indicated			X	As clinically indicated
Patient Oral Drug Administration Diary			Daily				
Correlative Studies							
Whole blood collected in STRECK tubes for cfDNA	Stratification sample sent to Foundation Medicine following registration		Days 1 and 15 of cycle 1, day 1 of cycles 2 and 3 and then prior to every 2nd cycle of treatment[9]	X[9]		X[14]	
PK Blood Collection			Day 15 of cycle 1[10]				
Archival tumour tissue[11]	Confirm available prior to registration	Submit within 4 weeks following enrollment					
Digital anatomical images upload for radiomics analysis and central radiology review.		All protocol mandated images must be uploaded to AGMednet[13]					
Adverse Events							
Adverse Events	To assess patient for eligibility as per 4.1.7	X	Continuously				X[2]
Quality of Life							
EORTC QLQ-C30 and NCI PRO-CTCAE		Within 7 days prior to enrollment	Day 1 of cycles 2-4 then at the time of imaging for disease assessment beginning with the 24 week assessment			X[12]	X[12] (required only at the 12 week follow-up visit if patient discontinued protocol treatment prior to PD and/or with related toxicities ≥ grade 3 and has not started new anti-cancer treatment)
Health Economics							
EQ-5D-5L		Within 7 days prior to enrollment	Day 1 cycle 3 then day 1 every other cycle		X[12]		At 3, 12, 24, 36, 48 and 60 months of follow up[12]
Resource Utilization Assessment			Each cycle			X[12]	X[12]

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1. A cycle is considered to be completed 28 days after IM administration of fulvestrant. The 4 week follow up visit is expected 4 weeks after the end of the last cycle.
2. Timing of disease assessment is calculated from date of enrollment. All patients will be seen at 4 weeks after the end of the last cycle date. Thereafter, patients will be followed every 12 weeks to document related ≥ grade 3 adverse events until resolved and survival status. For patients who discontinue protocol treatment with CR, PR, or SD ongoing, disease assessments must continue according to the protocol schedule until disease progression as per RECIST 1.1 criteria. Death report is required for all patients.
3. Bloodwork Timing: Pre-treatment physical exam and blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol. Day 1 assessments are required on day 1 of cycle 1.
4. Required every 12 weeks to follow ≥ grade 3 lab results related to protocol treatment until resolved.
5. Fasting glucose is required for eligibility (random glucose is not acceptable). Please instruct patients to fast for a minimum of 8 hours prior to blood collection. Fasting glucose is also required at subsequent time points, however, if it is determined that the patient is not fasting, please collect random glucose.
6. It is preferable that both amylase and lipase are assessed at the required time points. For sites where only 1 of these parameters is routinely measured, then either lipase or amylase is acceptable as long as the same investigation is performed throughout the duration of protocol treatment.
7. Urine or serum pregnancy test is acceptable. An ultrasound may be required to rule-out pregnancy.
8. For any patients who initiate home glucose monitoring as a result of treatment emergent hyperglycemia (see Section 7.3.2.2) a glucometer will be provided. Glucose values must be recorded in the Patient Glucose Monitoring Diary.
9. Correlatives blood sample should be collected within 28 days of objective disease progression. PD blood samples should also be collected if patient meets the criteria for objective disease progression after discontinuation of protocol treatment but prior to the start of a new anti-cancer treatment. On-treatment correlative blood samples can be taken at the same time as the pre-treatment blood draws (i.e. one day prior to day 1 of treatment where necessary).
10. Blood collection for PK is required on cycle 1 day 15 pre- and post- study drug dosing. The post-dose blood sample must be collected 2-4 hours after ipatasertib/placebo dose is taken. See Correlative Studies Manual for details.
11. Tissue must be confirmed available prior to registration for ALL patients. Archival tissue must be submitted at the same time that the baseline CRF is submitted. Refer to Section 12.1.
12. EORTC QLQ-C30, NCI PRO-CTCAE, EQ-5D-5L and Resource Utilization Assessment required until start of new anti-cancer treatment.
13. AGMednet access is provided to each site at the time of local activation.
14. Whole blood collection for cfDNA is required at the 4 week post-treatment follow up visit for all patients, including patients who have started a new anti-cancer treatment.

5.1 Follow-up for Ineligible Patients

The follow-up requirements for patients determined to be ineligible after enrollment but who have received no protocol therapy include submission of the Baseline Report and End of Treatment Report plus an annual short follow up form for survival. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 ENTRY/ENROLLMENT PROCEDURES

6.1 Entry Procedures

All registrations for screening/enrollments will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/enrolling patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the MA.40 trial specific web-site. If sites experience difficulties accessing the system and/or registering/enrolling patients please contact the help desk (link in EDC) or the MA.40 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG. The serial number will be assigned after registration for screening and will remain the same following enrollment.

The following information will be required at the time of registration for screening:

- trial code (CCTG MA.40)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking/optional consent version date
- confirmation of the requirements listed in Sections 4.0 and 5.0, including dates of essential tests and actual laboratory values

The following information will be required at the time of enrollment:

- confirmation of the additional requirements listed in Sections 4.0 and 5.0, including dates of essential tests
- stratification factors

6.2 Stratification

Subjects will be stratified by:

- PIK3CA/PTEN/ AKT1 status: altered versus wildtype/unknown.
- Prior treatment duration with CDK4/6 inhibitor: < 6 months versus ≥ 6 months.

6.3 Study Enrollment

There will be two steps for enrollment on this study, a registration for screening and an enrollment. Once the results of the cfDNA analysis for stratification are known, and all other eligibility criteria are confirmed, enrollment can take place. Both registration for screening and enrollment will be provided electronically.

At the time of registration for screening and enrollment, all data reported within the Patient Enrollment folder must be accurate, complete and verifiable against source documentation. If a system query is issued indicating that the patient is not eligible, registration and/or enrollment within the EDC system will not proceed. CCTG should be contacted for assistance if needed. Under no circumstances should inaccurate data be entered in order to permit registration for screening and enrollment.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws consent and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting screening/enrollment.

All enrolled patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 5.1.

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient enrollment.

7.1 Treatment Plan

7.1.1 *Drug Administration*

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	Ipatasertib	400 mg	PO	Day 1-21	1 cycle = 28 days
	Fulvestrant	500 mg	IM	Day 1 (+ day 15 of cycle 1 only)	
2	Placebo	matching	PO	Day 1-21	1 cycle = 28 days
	Fulvestrant	500 mg	IM	Day 1 (+ day 15 of cycle 1 only)	

A drug administration diary must be completed by the patient for each cycle of treatment with ipatasertib/placebo.

7.1.2 *Blinding / Un-blinding*

Blinding is critical to the integrity of this clinical drug trial. If there is a need to break the blind this must be discussed with the CCTG as per Appendix VIII.

7.1.3 *Premedication*

All patients will be pre-medicated with:

Agent(s)	Dose	Route	Duration	Schedule
Loperamide	2 mg	PO	Days 1-28 Cycle 1	BID

See Section 7.3.2.1 for further details regarding premedication with loperamide. Loperamide will not be supplied or reimbursed.

7.2 Dose Adjustments

Doses will be reduced or held for adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE v 5.0) (see Appendix IV).

Ipatasertib has been associated with identified risks including nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, AST increased, ALT increased, dehydration, decreased appetite, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatobiliary disorders, pneumonitis, colitis, and developmental toxicity.

Fulvestrant is associated with identified risks including injection site reactions (including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy), hepatotoxicity, asthenia, joint and musculoskeletal pain (includes arthralgia, and less frequently musculoskeletal pain, back pain, myalgia and pain in extremity), nausea, hypersensitivity reactions, rash, hot flushes, headache, reduced platelet count, vomiting, diarrhea, anorexia, and urinary tract infections.

The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

7.2.1 *Dose Modification for Ipatasertib/Placebo*

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation of ipatasertib/placebo as per dose reduction schedules (see below Table 1). If the patient does not tolerate the daily dosing of the ipatasertib/placebo, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib/placebo per patient will be allowed (see Table 1). The starting dose is 400 mg and two dose reductions are allowed, the first to 300 mg and the second to 200 mg. Dose re-escalation is not permitted for ipatasertib/placebo, regardless of the dose level.

Table 1: Dose Reductions for Ipatasertib/Placebo

Dose Level	Total Daily Ipatasertib/Placebo dose
Starting dose	400 mg
First dose reduction	300 mg
Second dose reduction	200 mg
Third dose reduction	Discontinue

7.2.2 *Dose Modification for Fulvestrant*

Dose reductions for fulvestrant are not required. Injections may be delayed at the discretion of the investigator to manage toxicity related to fulvestrant as described below and as per the most recent Product Monograph.

7.2.3 *Treatment Hold and Discontinuation*

Protocol treatment may be temporarily held in patients who experience toxicity considered to be related to study drug. If corticosteroids are initiated for treatment of the toxicity, they must be tapered to ≤ 10mg/day oral prednisone or equivalent before ipatasertib/placebo can be resumed, if clinically appropriate.

If treatment with ipatasertib/placebo must be held due to toxicity, treatment with fulvestrant should continue according to the schedule provided in Section 7.1.1. If ipatasertib/placebo has been withheld for > 56 consecutive days (2 cycles) because of treatment-related toxicity, the patient should be permanently discontinued from treatment with ipatasertib/placebo. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming ipatasertib/placebo after a hold of > 56 consecutive days, study drug may be re-started at the dose level approved by CCTG.

If treatment with fulvestrant must be held, treatment with ipatasertib/placebo may continue according to the schedule provided in Section 7.1.1 provided the duration of the hold for fulvestrant is less than 2 weeks. Dose holds for fulvestrant extending beyond 2 weeks must be discussed with CCTG before treatment can proceed.

Ipatasertib/placebo and/or fulvestrant treatment may be temporarily held/interrupted for reasons other than toxicity (e.g., surgical procedures) with approval from CCTG. If a scheduled fulvestrant dose coincides with a holiday or inclement weather or other conditions that preclude dosing, dosing should commence on the nearest following date, and, generally, subsequent dosing of both agents can continue on a new 28-day schedule on the basis of the new IM injection date.

In cases where treatment with ipatasertib/placebo is discontinued due to toxicity, patients may continue to receive treatment with fulvestrant at the discretion of the investigator. Patients who permanently discontinue treatment with fulvestrant should also discontinue treatment with ipatasertib/placebo except in cases where the patient is considered to be deriving benefit from ipatasertib/placebo monotherapy. These cases must be approved by CCTG before treatment can proceed.

7.3 Adverse Event Management Guidelines

Guidelines for management of specific adverse events are provided in the subsections below.

Management of adverse events related to fulvestrant should be made according to the most recent Product Monograph/approved label, with the exception of management of hepatotoxicity as outlined in Section 7.3.2.7.

7.3.1 *Management of Hematologic Toxicities*

The likelihood of hematological toxicities related to ipatasertib/placebo and fulvestrant is very low, therefore, specific dose modifications for hematologic toxicities are not provided. For toxicities ≥ grade 3, management according to Section 7.3.2.8 should be considered.

7.3.2 *Management of Non-hematologic Adverse Events*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) (Appendix IV)

7.3.2.1 *Diarrhea Management Guidelines*

All patients will be pre-medicated with loperamide 2 mg BID upon start of study treatment through the first cycle. Loperamide will not be supplied or reimbursed. After the first cycle, continued treatment with loperamide is encouraged for the remainder of the study or as needed. The prophylaxis dose of loperamide may be adjusted as necessary based on clinical judgement and per local guidance. Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions on treatment and prevention of dehydration so that patients can be promptly and appropriately managed.

Dose reductions of ipatasertib/placebo for diarrhea should only occur if the symptoms persist despite treatment with adequate anti-diarrheal medications. For diarrhea occurring after cycle 2 that persists for more than 5 days despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib / placebo, imaging to rule out colitis and/or a stool culture for infectious workup should be obtained.

Table 2: Diarrhea Management Guidelines

Severity of Diarrhea	Management Guidelines
Grade 1 Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Continue ipatasertib/placebo at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until 12 hour diarrhea-free interval. • Dietary modifications, such as avoiding lactose-containing foods and eating small meals and hydration with 8-10 glasses per day of clear liquid such as broth or low-calorie drinks with electrolytes.
Grade 2 Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	• Manage with loperamide as early as possible at 4 mg initially and then 2 mg every 4 hours or after every unformed stool until 12 hour diarrhea-free interval. • Dietary modifications such as avoiding lactose-containing foods and eating small meals and hydration with 8-10 glasses per day of clear liquid such as broth or low-calorie drinks with electrolytes. • 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. • Hold ipatasertib/placebo until diarrhea improves to ≤ grade 1. Ipatasertib/placebo can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to ≤ grade 1. • For recurrent grade 2 diarrhea, reduce ipatasertib/placebo by one dose level.
Grade 3 Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat as per grade 2 management guidelines and supportive care. • Hold ipatasertib/placebo until diarrhea improves to ≤ grade 1. Ipatasertib/placebo should be reduced by one dose level when treatment is restarted. • For recurrent grade 3 diarrhea, hold treatment as above and reduce ipatasertib/placebo dose by one additional dose level or permanently discontinue treatment as per investigator's discretion.
Grade 4 Life threatening consequences; urgent intervention indicated	• Management as per grade 3 guidelines. • Permanently discontinue ipatasertib/placebo.

7.3.2.2 *Hyperglycemia Management Guidelines*

Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination and blurred vision. As clinically indicated, the work-up for hyperglycemia should include fasting (abstaining from food or drink for ≥ 8hrs) blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, and hemoglobin A1C. Home glucose monitoring may be required based on the management guidelines below. Home glucose results may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g. random glucose value under 3.9 mmol/L) and hyperglycemia (e.g. random glucose value over 11.1 mmol/L). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. Increased glucose monitoring may include more frequent laboratory assessments in addition to home glucose monitoring using a glucometer as described in Table 3. For any patients performing home glucose monitoring, instructions must be provided regarding use of the glucometer and the frequency of the monitoring according to institutional guidance. Home glucose results must be recorded on the blood glucose log and this should be reviewed at each clinic visit (and source data retained). Entry of blood glucose results into the patient's eCRF will be limited to laboratory results only.

In the event of ipatasertib/placebo treatment hold/interruption, anti-diabetic medications may need to be held or reduced (per investigator judgment) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Guidelines for hyperglycemia attributable to ipatasertib/placebo are outlined below (see Table 3) based on fasting glucose measurements assessed in the clinic, unless otherwise specified. This table is not meant to inform grading of adverse events, which should be conducted per NCI CTCAE v5.0. All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects.

Table 3: Hyperglycemia Management Guidelines

Severity of Hyperglycemia	Management Guidelines
Fasting glucose value > ULN to 8.9 mmol/L	• Continue treatment with ipatasertib/placebo at current dose. • Consider oral anti-diabetic medications (e.g. metformin). • Consider home glucose monitoring under supervision of the treating investigator.
Fasting glucose value > 8.9-13.9 mmol/L	• Hold ipatasertib/placebo until fasting glucose values return to ≤ 8.9 mmol/L. • Initiate home glucose monitoring under supervision of the treating investigator. • Start oral anti-diabetic medications (e.g. metformin). • If patient is already taking oral anti-diabetic medication, the dose of ipatasertib/placebo should be reduced by one dose level when treatment is re-started. • If the patient previously had not been receiving oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Fasting or non fasting glucose value > 13.9 – 27.8 mmol/L	• Hold ipatasertib/placebo until fasting glucose values return to ≤ 8.9 mmol/L. • Initiate home glucose monitoring under supervision of the treating investigator. • 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). If the patient is already on oral anti-diabetic medication, ipatasertib/placebo should be reduced by one dose level when treatment is re-started. • If the patient previously had not been receiving oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If fasting glucose value exceeds 13.9 mmol/L again, the dose of ipatasertib/placebo should be reduced by one dose level when treatment is re-started.
Fasting or non-fasting glucose value > 27.8 mmol/L; life-threatening consequences; urgent intervention indicated	• Hold ipatasertib/placebo until fasting glucose values return to ≤ 8.9 mmol/L. • Initiate home glucose monitoring under supervision of the treating investigator. • 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). • Assess for volume depletion and appropriate intravenous or oral hydration. • Assess for diabetic ketoacidosis according to local guidelines. • Reduce ipatasertib/placebo by one dose level when treatment is re-started. • If fasting or non-fasting glucose value exceeds 27.8 mmol/L again, permanently discontinue ipatasertib/placebo.
NOTE: For all cases, the patient should receive education on a diabetic diet	

7.3.2.3 *Nausea and/or Vomiting Management Guidelines*

In general, patients should be closely monitored for GI effects and patients should be managed as per institutional standard of care and protocol guidelines, including hydration if appropriate, to prevent renal insufficiency due to fluid depletion. Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e. prochlorperazine or metoclopramide per institutional guidelines; see Table 4).

Table 4: Nausea and Vomiting Management Guidelines

Severity of Nausea and/or Vomiting	Management Guidelines
Grades 1 or 2	• Provide maximum supportive care as needed.
Grade ≥ 3	• Hold ipatasertib/placebo until nausea and/or vomiting resolves to ≤ grade 2. • Provide maximum supportive care as needed. • If grade ≥ 3 nausea or vomiting recurs, ipatasertib/placebo should be reduced by one dose level when treatment is re-started.

7.3.2.4 *Rash Management Guidelines*

Ipatasertib/placebo should be permanently discontinued for rash associated with Stevens Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in Table 5.

Table 5: Rash Management Guidelines

Severity of Rash	Management Guidelines
Grade 1	• Continue ipatasertib/placebo at current dose. • Consider treatment with topical corticosteroids.
Grade 2	• Hold ipatasertib/placebo treatment until resolution to ≤ grade 1 or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids. • Reduce ipatasertib/placebo by one dose level for recurrent grade 2 rash.
Grade 3	• Hold ipatasertib/placebo treatment until resolution to ≤ grade 1 or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If, within 28 days, the skin toxicity resolves to ≤ grade 1 or is no longer clinically significant within 28 days, following completion of steroid taper, ipatasertib/placebo may be resumed at one dose level below the previous dose. • If skin toxicity remains clinically significant continuously for 28 days, or grade 3 rash recurs, permanently discontinue ipatasertib/placebo.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. • Consider dermatological consultation and skin biopsy. • Ipatasertib/placebo should be permanently discontinued.

7.3.2.5 *Pneumonitis Management Guidelines*

Pneumonitis is not known to be causally related to ipatasertib, however, pneumonitis has been observed with drugs that target pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 6).

Table 6: Interstitial Lung Disease/Pneumonitis Management Guidelines

Severity of ILD/Pneumonitis	Management Guidelines
Grade 1	• Continue ipatasertib/placebo at current dose. • Perform CT scan. Repeat CT scan every 8 weeks until a return to baseline. Pulmonary function tests are suggested to establish a baseline.
Grade 2	• Prescribe corticosteroids, as clinically indicated, once infectious etiology is ruled out. Hold ipatasertib/placebo treatment while patient is treated with corticosteroids. • Perform CT scan and pulmonary function tests. Repeat CT scan every 4 weeks until a return to baseline. • If pneumonitis resolved to grade ≤ 1 after completion of steroid taper, ipatasertib/placebo may be resumed at either the previous dose or reduced by one dose level per investigator discretion. • For recurrent grade 2 pneumonitis, ipatasertib/placebo must be resumed at one dose level below the previous dose. • Discontinue ipatasertib/placebo if recovery to grade ≤ 1 is not evident within 28 days.
Grade 3	• Prescribe corticosteroids, as clinically indicated, once infectious etiology is ruled out. Hold ipatasertib/placebo treatment while patient is treated with corticosteroids. • Perform CT scan and pulmonary function tests. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is also recommended. • If pneumonitis resolves to grade ≤ 1, following completion of steroid taper, reduce ipatasertib/placebo treatment by one dose level. • Discontinue ipatasertib/placebo if recovery to grade ≤ 1 is not evident within 28 days. • For recurrent non-infectious grade 3 pneumonitis, ipatasertib/placebo should be permanently discontinued.
Grade 4	• Prescribe corticosteroids, as clinically indicated, once infectious etiology is ruled out. • Permanently discontinue ipatasertib/placebo. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is also recommended.

7.3.2.6 *Mucositis Management Guidelines*

Mouthwash such as magic mouthwash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table 7.

Table 7: Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If grade ≥ 2 mucositis recurs in subsequent cycles despite maximal supportive care, the dose of ipatasertib/placebo should be reduced by one dose level.
Grade ≥ 3	• Hold ipatasertib/placebo until recovery to ≤ grade 2. If mucositis resolves to ≤ grade 2, the dose of ipatasertib/placebo should be reduced by one dose level.

7.3.2.7 *Hepatotoxicity Management Guidelines*

Permanently discontinue ipatasertib/placebo for any patients who develop a concurrent elevation of ALT and/or AST to ≥ 3 x ULN and total bilirubin ≥ 2 x ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria.

Table 8: Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guidelines
Grade 1: AST or ALT > ULN – 3.0 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal *or* Total bilirubin > ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 X baseline if baseline was abnormal	• Continue ipatasertib/placebo and fulvestrant at current dose level. • Monitor LFTs according to protocol schedule
Grade 2: AST or ALT > 3.0 – 5.0 x ULN if baseline was normal; > 3.0 – 5.0 x baseline if baseline was abnormal *or* Total bilirubin > 1.5 – 3.0 x ULN if baseline was normal; > 1.5 – 3.0 X baseline if baseline was abnormal	• Continue ipatasertib/placebo and fulvestrant at current dose level. • The frequency of LFT monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.

table continues on next page …

Severity of LFT Elevation	Management Guidelines
Grade 3: AST or ALT > 5.0 – 20.0 x ULN if baseline was normal; > 5.0 – 20.0 x baseline if baseline was abnormal *or* Total bilirubin > 3.0 – 10.0 x ULN if baseline was normal; > 3.0 – 10.0 x baseline if baseline was abnormal	• Hold ipatasertib/placebo and fulvestrant. • On return of LFTs to ≤ grade 2, restart ipatasertib/placebo and fulvestrant at previous dose level. • Consider hepatology consult. • Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. • If another grade 3 event occurs, hold treatment with ipatasertib/placebo and fulvestrant. On return of LFTs to ≤ grade 2, restart ipatasertib/placebo reduced by one dose level. Fulvestrant may be resumed at the original dose. • Permanently discontinue treatment with ipatasertib/placebo and fulvestrant for further grade 3 occurrences.
Grade 4: AST or ALT > 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal *or* Total bilirubin > 10.0 x ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal	• Permanently discontinue treatment with ipatasertib/placebo and fulvestrant.

7.3.2.8 *Management of Other Clinically Significant Adverse Events*

If other Grade ≥ 3 toxicities not described above develop in patients, ipatasertib/placebo may be held at the discretion of the investigator. During this time, treatment may continue with fulvestrant. Grade ≥ 3 clinically significant toxicity should be monitored at least weekly. If the toxicity is deemed related to ipatasertib/placebo and resolves to Grade 1 or better in 2-4 weeks, the dose of ipatasertib/placebo should be reduced by one level per the suggested guidelines in Table 1.

For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only (e.g. lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis), study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional guidelines.

7.4 Duration of Therapy

Patients should continue protocol treatment until RECIST 1.1 defined progression or unacceptable toxicity/other treatment discontinuation criterion is met. See Section 10.0 for further details on protocol discontinuation criteria.

7.5 Concomitant Therapy

7.5.1 *Permitted*

- Medications required to treat adverse events, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics, anti-diarrheal medications (refer to section 7.3.2.1) as well as medical marijuana/cannabis oil/commercially procured marijuana, taking into account those not permitted below.
- Bisphosphonates / denosumab are permitted for the treatment of hypercalcemia, osteoporosis and prevention of skeletal related events for patients with bone metastases.
- LHRH agonists/antagonists are permitted only for pre-menopausal women as per eligibility criterion 4.1.2.
- Moderate CYP3A4 inhibitors should be taken with caution as they can increase ipatasertib exposure (see Appendix VII).

7.5.2 *Not Permitted*

- Strong CYP3A inhibitors: such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements (see Appendix VII).
- Strong CYP3A inducers: such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin (see Appendix VII).
- CYP3A4 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.
- Herbal medications/preparations, dietary supplements that are potentially hepatotoxic or with known or potential drug interactions.
- Administration of any other anti-cancer therapy is not permitted while the patient is receiving protocol therapy. Patients may be treated at the investigator's discretion after discontinuation of protocol therapy. Specifically, with respect to concurrent radiation therapy while on protocol treatment:
  - Radiation therapy to a solitary non-target lesion (i.e. for symptomatic pain relief) may be permitted after consultation with CCTG
  - Radiation therapy to target lesions is not permitted while the patient is receiving protocol therapy. Patients who require radiation therapy to a target lesion would be considered to have met the criteria for disease progression and discontinuation of protocol treatment is required.
- Systemic corticosteroids > 10 mg daily oral prednisone equivalent (except as stated in Section 7 to treat a protocol treatment related adverse event or for pre-medication for contrast allergy as per local guidelines).

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

All enrolled patients will be evaluable for baseline adverse events and adverse events on treatment from the time of their first treatment..

8.1.2 *Evaluable for Response*

All enrolled patients will be included in the analyses of response. Those patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*.

8.1.3 *Evaluable for Quality of Life Assessment*

All enrolled patients who have completed the quality of life questionnaire are evaluable for quality of life analyses.

8.1.4 Evaluable for Health Economics Assessment

All enrolled patients are evaluable for health economics analyses. All patients who have completed the health utility questionnaire will be evaluable for cost-utility analyses.

8.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee *[Eisenhauer, 2009]*.

8.2.1 *Measurable Disease*

Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

8.2.5 *Response*

8.2.5.1 *Patients with Measurable Disease*

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer, 2009]* before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden appears to have increased by at least 73% in volume, or in select instances where tumour burden has increased sufficiently to require urgent intervention (e.g. radiation for spinal cord compression or drainage of a fluid collection). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Tumour nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Tumour nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic progression". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

8.2.5.2 *Patients with Non-Measurable Disease Only*

Patients with only non-measurable (but evaluable) disease, may only have an overall RECIST 1.1 response of CR, non-CR/non-PD or PD as follows:

Complete Response (CR): disappearance of non-target lesions. Residual lesions thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]* before CR can be accepted.

Non-CR/Non-PD: persistence of one or more non-target lesion(s).

Progressive Disease (PD): the appearance of new lesions and/or unequivocal progression of non-target lesions.

Table 2: Integration of Non-Target and New Lesions into Response Assessment for patients with only non-measurable, evaluable, lesions:

Non-Target Lesions*	New Lesions	Overall Response	Best Overall Response for this category also requires
CR	No	CR	
Non-CR/Non-PD	No	Non CR/ Non-PD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	No	NE	
Unequivocal PD**	Yes or No	PD	No prior CR or non-CR/non-PD
Any	Yes	PD	

* Note that these lesions should be recorded under the "Non-Target" lesions table on the CRFs.

** Unequivocal progression in non-measurable lesions will be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic progression". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

8.3 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

8.4 Stable Disease Duration

Stable disease duration will be measured from the time of enrollment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.5.1 *Clinical Lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.5.2 *Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.5.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer, 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.5.4 *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.5.5 *Endoscopy, Laparoscopy*

The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.5.6 *Cytology, Histology*

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAEs) defined as per ICH guidelines (see below) and other adverse events must be reported on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

Adverse Event Reporting

Adverse event reporting for this trial will be as follows:

- All adverse events will be captured on the case report form as follows:
  - Baseline: all adverse events experienced within 14 days prior to start of protocol treatment.
  - During protocol treatment and up to 4 weeks after discontinuation of protocol treatment: all adverse events.
  - During follow up: all ≥ grade 3 AEs which are new or ongoing and related to protocol therapy until complete resolution.

- Adverse Events of Special Interest (AESI), applicable to ipatasertib/placebo and fulvestrant, will require expedited reporting using the AESI report (if not serious) or SAE report (if serious). AESIs which are not SAEs must also be reported according to the timelines outlined in Section 9.2. AESIs collected for this trial are as follows:
  - 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.
  - Grade ≥ 3 hepatotoxicity.
  - Grade ≥ 3 ALT/AST elevations.
  - Suspected transmission of an infectious agent by the study drug, defined as 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.
  - Grade ≥ 3 diarrhea.
  - Grade ≥ 3 fasting hyperglycemia.
  - Grade ≥ 2 pneumonitis.
  - Grade ≥ 2 colitis/enterocolitis.
  - Grade ≥ 3 rash.
  - Erythema multiforme.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring from the first protocol treatment administration until 30 days after last protocol treatment administration and at any time afterwards. Note: adverse events which occur prior to the start of protocol therapy must only be reported as serious adverse events if they are directly related to a study specific procedure.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure or product monograph.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death;
  - is life-threatening;
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care);
  - results in persistent or significant disability or incapacity;
  - is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the MA.40 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.
Within 10 days:	Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

MA.40 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the MA.40 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.12. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 2 years after the last dose of study drug must also be reported.

The investigator should report the pregnancy within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the “Toolbox” link. The Pregnancy Reporting Form should be updated to provide the outcome of the pregnancy.

Information from the trial participant’s pregnant partner can only be collected following informed consent. A copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG. Centres that require additional informed consent to collect information about the pregnancy from a trial participant must submit a copy of the signed signature page of the pregnancy follow-up consent to CCTG.

All follow-up reports must be submitted to CCTG in a timely manner. All documents must be sent to the CCTG safety desk (Fax: 613-533-2812/Email: safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an ‘inpatient hospitalization’ for the purposes of pregnancy reporting.

9.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage, under the "Toolbox" link.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual 30 days following the exposure. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (Fax: 613-533-2812/Email: safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.3.4 *Blinded Studies and Patient Unblinding*

Centre requests for participant unblinding as a result of a pregnancy or exposure are acceptable. However, the usual unblinding rules (see Appendix VIII) must be followed.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.5 CCTG Responsibility for Reporting Serious Adverse Events to Breast Cancer Trials Australia

The CCTG will provide expedited reports from Australia and New Zealand of SAEs for those events which meet the regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out) to the MA.40 trial team at Breast Cancer Trials (BCT) for reporting to other regulatory authorities.

9.6 CCTG Reporting Responsibility to Hoffman-La Roche Ltd.

Hoffman La-Roche Ltd. will be notified of all protocol reportable serious adverse events, adverse events of special interest, special situation reports and instances of exposure to study drug during pregnancy or lactation within agreed timelines.

9.7 Hoffman-La Roche Reporting Responsibilities

Hoffman La-Roche Ltd. shall notify CCTG of individual safety reports from other studies using ipatasertib, which may affect the overall safety profile of the study and which they have reported to Health Canada.

9.8 Reporting Safety Reports to Investigators

For Canadian Sites:
CCTG will notify Investigators of all Safety Reports including all serious adverse events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment (SUSARs) from this trial as well as Safety Updates (single reports or line listings).

The reports will be posted to the CCTG trial MA.40 web-based safety monitoring utility, available on the CCTG trial webpage, under the "Toolbox" link. Relevant safety reports requiring REB submission that are not submitted at the time of initial REB approval should be submitted to the REB as soon as possible (suggest within 30 days of the date of local activation). REB submissions greater than 90 days from the date of local activation will be regarded as delinquent and a major deficiency will be assigned. Centres being activated later in the life of the study only need to submit the latest version of the IB/PM and safety reports as described above.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the Safety Report such as protocol and/or informed consent changes. Safety reports that are not mandated by CCTG to be submitted to the REB are marked as "NR" (not required) in the safety report monitoring utility. However, local policy may still require REB submission of this information.

The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial MA.40 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0.
- Request by the patient.

Note: Efforts must be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

If patients discontinue protocol treatment due to adverse events or progression of disease, any further non-protocol treatment is at the discretion of the investigator.

10.3 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy (4 weeks after the end date of the last cycle) then every 12 weeks thereafter. For patients who discontinue protocol therapy with CR, PR or SD ongoing, disease assessments will continue during follow up as per the protocol schedule until disease progression. New or ongoing adverse events experienced during follow up which are ≥ grade 3 and related to protocol therapy must be documented until complete resolution. A Death Report will be required for all patients.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

The CCTG Central Data Review process is a critical part of CCTG's quality assurance program. As part of this trial, limited critical data will be collected by CCTG, including de-identified surgical reports, digital images and reports and pathology reports to allow central data review and confirmation of eligibility (disease under study) and primary outcomes (including date of progression). These reviews and confirmations will be performed by experts (e.g. CCTG Central Office, Trial Committee) and are critical to ensuring the accuracy of the data and consistency of conclusions drawn, thus reducing bias.

The collection of this critical data involves uploading documents through the electronic Supporting Document Upload Tool (SDUT) data capture linked system. See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are removed and the site assigned a violation and required to resubmit.

All patients will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

11.2 Central Radiology Review

A radiology review of all cases by a third party is planned to confirm response to treatment. The upload of digital images and clinical photography of skin lesions is required to conduct this review. The reviewer will be blinded to study treatment allocation. Details of electronic upload of imaging files will be provided to sites by the third party.

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

Collection and immediate shipment of time sensitive samples (e.g. cfDNA for stratification) MUST occur after registration. This is to ensure that the stratification samples are labelled with a CCTG patient ID, which is required for return and entry of results.

A detailed Correlative Studies Manual will be provided on the MA.40 trial specific website, which will include details regarding sample preparation, handling and shipping.

Correlative samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The identification of samples may include a patient study number assigned at the time of registration to the trial, a surgical/ histology number, patient initials and year of birth. Material issued to researchers will be anonymized and only identified by a coded number.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

Genetic Testing

In the course of genetic testing for this study, there is a chance that "clinically relevant incidental findings" may occur; these refer to unanticipated discoveries made in the course of research but that are outside of the scope of the research *[TCPS2 2014]* being conducted. These findings could be inherited changes that might predispose a person to particular cancers or other diseases, and may be passed on in families.

As the genetic testing for this study will be conducted in a certified laboratory the results will be considered validated.

During the informed consent process, participants will be told about the remote possibility of clinically relevant incidental findings being discovered, and given the opportunity to make informed choices about whether they wish to receive this information.

If a clinically relevant incidental finding is discovered during the testing for this study and a participant consented to learning about the results, the enrolling institution will be responsible for following local SOPs with regard to confirming the result, ensuring genetic counseling is available, obtaining REB approval (if required) and contacting the study participant.

12.1 Protocol-Mandated Correlative Studies

The goal of the correlative studies component of the trial is to genomically profile the emergence of clinical resistance to ipatasertib treatment. The objective is to capture quantifiable genomic, epigenomic and proteomic longitudinal alterations, that when integrated with response data will facilitate the development of prognostic and predictive biomarkers related to ipatasertib sensitivity.

Pharmacokinetic studies will also be conducted.

Blood Collection (Mandatory)

The submission of whole blood is mandatory for participation in this trial. Whole blood will be collected at the following time points:

- at the time of patient registration for stratification
- on days 1 and 15 of cycle 1
- on day 1 of cycles 2 and 3 then prior to every 2nd cycle of treatment
- at the time of objective disease progression
- 4 weeks after discontinuation of protocol treatment

Blood samples for stratification will be analyzed by Foundation Medicine using the FoundationOne® Liquid platform. Following analysis of the stratification sample by Foundation Medicine, an alteration report will be provided to the investigator. The expected turnaround time for the report is 14 days from the date that the sample is received by Foundation Medicine. The investigator will be responsible for entering the alteration result for stratification and enrollment based on the report provided.

The following alterations will be considered alteration positive for stratification:

- AKT1 alterations that result in an amino acid substitution at the E17, L52 or Q79 residues
- PIK3CA alterations that result in an amino acid substitution at the R88, G106, K111, G118, N345, C420, E453, E542, E545, Q546, M1043, H1047 or G1049 residues
- PTEN dominant negative SNV (C124S, G129E, R130X) or homozygous deletion (copy number of 0)

cfDNA samples from baseline, on treatment, at the time of disease progression, and at 4 weeks post-treatment will be evaluated using established targeted sequencing methods and technologies such as Foundation One® Liquid and the OICR MA.38 (NCT02630693) bespoke panels. The MA.38 panel was specifically designed to address key signaling features in CDK4/6 pathway resistance (e.g. CCNE1) *not* currently included on Foundation One® Liquid. Further features specific to PIK3CA pathway assessment (potentially including TSC1/2, HK & NRAS) may mandate a similar approach in MA.40. These techniques allow for significant genomic depth to confidently identify tumour-derived mutations whose variant allele fraction in tumours are $\geq 0.2\%$. Included in this approach is an assessment of tumour mutational burden (TMB) and microsatellite instability.

Specifically, PFS will be compared between patients exhibiting altered/mutant PI3K/PTEN/AKT1-3 cfDNA and those with unaltered cfDNA, relative to treatment. In addition, using the cfDNA samples collected during treatment, alterations of cfDNA and emergence of "novel" mutations (for example PIK3CB, which is mutated in 1-2% of breast cancers) will be identified and assessed with respect to therapeutic response and potentially requiring a "bespoke" cfDNA panel. cfDNA analysis performed upon progression or end of treatment will be employed to identify patterns of genomic alterations and possible underlying mechanisms associated with resistance to ipatasertib (and fulvestrant).

DNA and RNA will be isolated from blood-derived exosomes for genomic and transcriptomic analysis, respectively, and proteins will be extracted for characterization using mass spectrometry based techniques. Exosomal contents at baseline will be evaluated to identify potential prognostic and predictive genomic/transcriptomic/protein features and key pathways linked to ipatasertib sensitivity. Samples collected during treatment will be used to assess emergence of "novel" exosomal alterations with respect to therapeutic response, and those collected at progression will be useful in identifying alterations associated with resistance to ipatasertib (and fulvestrant).

Pharmacokinetics (Mandatory)

Blood samples will be collected to enable pharmacokinetic correlations with response and safety. Blood samples will be collected on all patients pre- and post-ipatasertib dose (2-4 hours) on day 15 of cycle 1. Please refer to the correlative studies manual for further details regarding collection and processing of the pharmacokinetic samples.

Tumour Tissue Collection (Mandatory)

The submission of a representative block of the diagnostic tumour tissue is mandatory for participation in this trial. One tumour block is requested from the most recent biopsy or resection. Tumour tissue from a metastatic lesion is preferred, however tissue from the primary site is also acceptable. Where local centre regulations prohibit submission of blocks of tumour tissue, cores (two 2 mm cores of tumour from the block) or 20 slides of representative tumour tissue may be substituted instead.

Where no previously resected or biopsied tumour tissue exists or is found to be of inadequate amount or quality, an additional biopsy of the metastatic or primary tumour will be required for the patient to be considered eligible for the study.

Dual DNA/RNA extraction will be performed on the diagnostic FFPE tumour material. We will perform quantitative expression profiling using technologies such as the NanoString gene expression profiling or RNA sequencing. Both technologies enable highly sensitive and reproducible digital profiling of RNA from small amounts of FFPE material. We will evaluate expression of key cancer pathways and processes. Employing state-of-the-art analytical methods, including machine learning, we will identify prognostic and predictive transcriptomic features and key pathways linked to ipatasertib sensitivity. Tumour FFPE samples will also be evaluated for genomic aberrations using NGS platforms and concordance between alterations in the primary tumour and the cfDNA alterations detected above will also be evaluated.

With respect to PTEN, a key mediator of sensitivity to CDK4/6 inhibitors and potential effector of ipatasertib sensitivity, expression will be evaluated by RNAseq and possibly traditional IHC. Targeted methylSeq will also be utilized as promoter methylation is a common cause of reduced PTEN protein expression in numerous cancer types. PTEN expression (low vs non-low) will also be incorporated into the analysis of progression free survival described above (altered/mutant PI3K/PTEN/AKT1 vs unaltered), however, this will be evaluated for exploratory purposes outside of the parameters defined for stratification by the FoundationOne® Liquid platform.

As an extension of the PTEN promoter methylation analysis, additional methylation profiling will be implemented using a targeted sequencing panel to identify clinically relevant epigenomic features. This approach uses the bisulfite method for identifying specific methylation patterns within a DNA or FFPE DNA sample. With low DNA input (10-20ng), (the panel provides high accuracy and can detect methylation status of a minimum of 38 targets.

Genomic/transcriptomic changes within the primary tumour FFPE material will also be evaluated for possible associations with time on CDK4/6 inhibitor treatment, since all patients will have received CDK4/6 based therapy before enrollment. Critical effectors of CDK4/6 inhibitor sensitivity such as Rb, CCNE and CCND1 will be a focus of this evaluation and this will be reflected in the techniques used for analysis.

Proteomic characterization will be performed on FFPE tumour tissue using IHC and NanoString's GeoMx® digital spatial profiling to evaluate possible correlations with progression free survival. The DSP platform allows the interrogation of multiple proteins within multiple defined areas (tumour vs stroma). We will evaluate changes in expression of key immune cell types including T cells, B cells and macrophages, checkpoint molecules and immune function. Other possible platforms for proteomic analysis will also be considered, including mass spectrometry/cytometry.

Digital Imaging Collection (Mandatory)

Digital images from all time points must be uploaded in order to conduct the central radiology review and radiomics analysis. Images must be de-identified according to local SOPs prior to upload. If de-identification of images is not possible, please contact CCTG. For the radiomics analysis, mathematical methods will be applied to derive information including gray-level intensity, pixel inter-relationships and spectral properties of the images which may be imperceptible to the human visual system *[Davnall 2012]*. The goals of the planned radiomic analyses include prognostication of outcome, prediction of response to endocrine therapy and ipatasertib and characterization of patterns of resistance to therapy, independent of traditional imaged based methods of estimation of tumour response/progression using RECIST 1.1.

A detailed manual will be provided by the third party reviewer, which will include details regarding image upload.

12.2 Optional Banking

Banking of Tumour Tissue

Mandatory submission of tumour tissue has been described above. The subsequent banking of any remaining tissue is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

Biomarker Research on Tumour Tissue and Blood Samples

As researchers become aware of new prognostic and predictive information related to ipatasertib activity, additional research outside of the planned assays may be applicable. Patients will be asked to consent to the use of tumour tissue and blood samples for additional assays not listed in the protocol. The results of this research will be used to better understand how patients are affected by the study treatments. This is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. No additional sample collection is required for this purpose and the samples used will have already been sent to the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

Banking of Digital Images

Mandatory upload of de-identified digital images and clinical photography of skin lesions for central radiology review and radiomics analysis has been described above. The subsequent banking of the digital images is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Digital images will be collected by a third party and then transferred to CCTG for banking following central review. Images from patients who have consented to banking will be stored indefinitely at Queen's University in Kingston, Ontario.

Proposals to use the banked digital images for research purposes may be submitted to CCTG. A scientific review process of any proposals to use the digital images will take place and any proposals approved will have undergone ethics approval.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

The primary objective of this trial is to compare progression-free survival (PFS) in the intent to treat (ITT) population consisting of enrolled patients with ER+/HER- advanced/metastatic breast cancer and treated with ipatasertib and fulvestrant versus placebo and fulvestrant after progression on first line CDK 4/6 inhibitor plus AI treatment.

A key secondary objective is to compare PFS between the two treatment arms in the subgroup with PIK3CA/AKT1/PTEN altered status. Other secondary objectives include response rate, duration of response, clinical benefit rate, overall survival, time to commencement of subsequent systemic therapy or death, quality of life, health economics and safety comparisons between the two treatment arms in the ITT population.

Eligible subjects will be randomized at 1:1 ratio to one of the following two treatment groups: ipatasertib + fulvestrant (experimental arm) or placebo + fulvestrant (control arm). Subjects will be stratified by: 1) PIK3CA/PTEN/AKT1 alteration status: altered versus wildtype/unknown, 2) prior duration of treatment with CDK 4/6 inhibitor: < 6 months versus ≥ 6 months.

13.2 Primary Endpoints and Analyses

The primary endpoint is progression-free survival (PFS) defined as time from randomization to disease progression or death from any cause, whichever occurs first. Disease progression will be investigator assessed using the RECIST 1.1 criteria *[Eisenhauer, 2009]* CCTG or its designee will collect and store all tumour measurement images on all enrolled patients throughout the study to enable an independent review of imaging scans and an assessment of disease progression. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last visit with adequate disease assessment. Lack of tumour assessments post-randomization will lead to censoring at the date of randomization. Progression documented between scheduled visits will be assigned to the date of the clinical lesion evaluation indicating progression. Death before first PD assessment, including death between adequate assessment visits, will lead to the assignment of progression to the date of death. Death or progression after more than one missed visit will lead to the censoring of data at the date of last visit with adequate assessment.

The primary PFS comparison between treatment arms will be performed on data derived from the ITT population. All patients will be included in the primary PFS efficacy analyses according to the arm of randomization, regardless of the actual treatment received. The PFS survival experiences of subjects in both treatment arms will be described by the Kaplan-Meier method. Stratified two-sided log-rank tests adjusting for stratification factors as defined in the protocol will be the primary method to compare PFS between experimental and control arm. As an exploratory analysis, a Cox proportional hazards model will be used to identify and adjust for factors significantly related to progression free survival.

A pre-specified secondary analysis for PFS in the PIK3CA/PTEN/AKT1 altered status subset will be tested using a hierarchical testing procedure *[Hung, 2007]*. If the result for PFS in the ITT patient population is significant at a 0.05 level, then PFS will be tested in the PIK3CA/PTEN/AKT1 altered status subset under the same 0.05 significance level. If this criterion for the PFS comparison is not met in the ITT population, no further testing for the PFS comparison will be performed in the PIK3CA/PTEN/AKT1 altered status subgroup.

13.3 Secondary Endpoints and Analyses

All efficacy endpoints will be compared between arms in the ITT population with exploratory analyses in the PIK3CA/PTEN/AKT1 altered status and/or wildtype/unknown.

Response rate (RR) per RECIST 1.1 is defined as the number of responders (complete response and partial response) as a percentage of all the randomized patients. The 95% confidence intervals for the response rate will be calculated for each arm. The difference of response rate between two arms and the corresponding 95% confidence interval will be obtained by the asymptotic normal approximation.

Duration of Response (DoR) will be calculated for patients with a best response of CR or PR as per RECIST 1.1 criteria. DoR is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. A Kaplan-Meier analysis of duration of response will be performed to describe the experience of both treatment arms.

Clinical Benefit Rate (CBR) will be calculated for patients with a best overall response of CR, PR or SD (≥ 6 months) as per RECIST 1.1 criteria as a percentage of all randomized patients. The 95% confidence intervals for the CBR will be calculated for each treatment arm. The difference of CBR between the two treatment arms and the corresponding 95% confidence interval will be obtained by the asymptotic normal approximation.

Overall Survival (OS), defined as time from randomization to the time when death from any cause is documented, will be analysed similar to PFS.

Time to commencement of subsequent line of systemic therapy or death (TSST) is defined as time from randomization to the time of subsequent treatment commencement or death, whichever comes first. TSST will be censored at the date of last known alive without commencement of subsequent line of systemic therapy. TSST will be analyzed similar to the PFS endpoint using the time-to-event methods such as the KM curves and stratified long-rank test.

The safety population will consist of patients who received at least one dose of study treatment, and will be based on the actual treatment received if this differs from randomized treatment assignment. All subjects will be evaluated for toxicity from the time of their first dose of study medication. Toxicities will be graded using the CTCAE version 5.0. The incidence of toxicities by treatment will be summarized by type of adverse event and severity. A Fisher's Exact Test will be used to compare selected toxicities between two arms.

Quality of Life and Health Economics analyses are defined in Sections 13.7 and 13.8.

13.4 Sample Size and Duration of Study

The statistical assumptions for the control arm are based on the median PFS of 4.8 months in the control arm of FAKTION (though no prior CDK 4/6 inhibitor exposure in this trial) and the median PFS of 5.6 months in the control arm of SOLAR-1 (6% prior CDK 4/6 inhibitor exposure). Thus we assume an H_0 median PFS of 4.5 months for the placebo + fulvestrant arm. Assuming a projected hazard ratio (HR) of 0.60 of benefit and thus a projected median PFS of 7.5 months in the ipatasertib and fulvestrant arm (H_1 median PFS of 7.5 months) with an $\alpha = 0.05$ (2-sided) and 92% power, a total of 250 randomized patients (ITT population) will be required. The duration of enrolment will be 24 months with 30 additional months for follow-up for the secondary and overall survival end points. A total of 175 events will be required to trigger the final analysis for PFS, which is estimated to occur 6 months after the final patient is enrolled. If PFS is significant for the ITT population at 0.05 level, then the pre-specified secondary analysis for the altered subgroup will be conducted. Assuming that the incidence rate of mutations is 45% and two-sided alpha = 0.05, the power to detect a hazard ratio of 0.50 (median PFS 3.5 months versus 7.0 months) will be 87% with a total of 79 PFS events.

For the secondary endpoint of OS, it is estimated that 76 deaths will have occurred at the time of the final PFS analysis. This will provide 34% power to establish an OS benefit with an assumed HR of 0.70 for OS. This projection is based on an estimated median OS in the control arm of 30 months and a projected median OS of 42.86 months in the ipatasertib + fulvestrant arm.

An additional OS analysis is planned when 155 deaths are observed. This will provide 60% power to establish an OS benefit with an assumed HR of 0.70 for OS (duration of follow-up of 30 months). These projections are based on an estimated median OS in the control arm of 30 months and a projected median OS of 42.86 months in the ipatasertib + fulvestrant arm.

13.5 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

The CCTG Data Safety Monitoring Committee (DSMC) will review progress and safety data (including SAEs and fatal SAEs) bi-annually.

13.6 Interim Analysis

No interim analysis is planned for this study.

13.7 Quality of Life Analysis

Scoring of the EORTC QLQ-C30 will be done according to the scoring manual. Missing questionnaires will be calculated and the proportion of expected questionnaire completion at each time point will be reported. Management of missing data within questionnaires will follow the scoring manual. Standard CCTG statistical analysis for QOL/PRO will be done *[Osoba, 2005]*

For the PRO-CTCAE, item responses are scored from 0 to 4 and there are no guidelines on how to combine the scores for a symptom nor for the longitudinal analysis. Developers recommend that the data should be reported at least descriptively at a minimum and along with the CTCAE grades for the corresponding period. The proportion of missing data should also be summarized (https://healthcaredelivery.cancer.gov/pro-ctcae/faqs.html).

For the main QOL analysis, we will compare the difference in overall QOL between baseline and 8 weeks between the 2 treatment arms. We hypothesized that if there is improved PFS in the combination arm of ipatasertib and fulvestrant, there will be no worsening in overall QOL.

With a sample size of 200 patients (based on an estimate of 20% non-compliance to questionnaire completion), we will have a 80% power with a 2-sided alpha error of 5% to detect an effect size of 0.40 for the difference in overall QOL on the EORTC QLQ-C30 at 8 weeks.

We will not adjust for multiple comparisons for the other comparisons of other EORTC QLQ-C30 subscales or PRO-CTCAE symptoms.

The mean and standard deviation of each QOL domain/item score at baseline and mean and standard deviation of QOL change score from baseline at each assessment time will be calculated. Then Wilcoxon Rank-Sum test will be used to compare the two treatment arms in terms of change in QOL score at each assessment time from baseline.

The profile of change scores over time for diarrhea, rash, fatigue and pain between the treatment arms will be compared using a generalized linear mixed model. The presence of a treatment by time interaction will be tested if the interaction effect is significant, treatment differences will be tested at each time point.

Four specific symptoms/toxicities from the PROCTC AE will be compared between the treatment arms: diarrhea, rash, fatigue and pain. These will be compared using the Fisher's exact test.

13.8 Health Economics Analysis

We will embed an economic evaluation nested within the trial framework to determine the incremental costs and benefits (life years, quality adjusted life years) across the two treatment arms. This analysis will be performed from both a health system and a societal perspective.

The economic evaluation will estimate the model outcomes within the trial period, and a subsequent modelled analysis will be performed to estimate the costs and outcomes beyond the period of the trial over the estimated lifetime of the study participants. Additional data inputs from the modelled analysis that are unavailable through the trial will be estimated from the published literature and from expert consultation. Cox proportional hazards regression will be used to estimate survival endpoints to allow for the adjustment of different follow-up and survival among participants. Uncertainty will be characterized using 95% confidence intervals and non-parametric bootstrapping methods. Due to the potential that time-preference could drive both the costs and benefit, a standard discount rate of 5% will be applied to both and will be subject to sensitivity analysis. The discount rate as well as other potential drivers of costs and benefit will additionally be evaluated in one-way sensitivity analyses.

Cost estimates will be based on both the health system and societal resources utilized by subjects in the trial. Health system resources will be identified as, but not limited to, clinic visits, treatments (radiation, surgery), physician encounters, hospitalizations related to treatment and complications, emergent visits and diagnostics. These resources will be based on the trial protocol and data collected during the trial itself. Societal resources will be identified as, but not limited to, lost productivity related to treatment (e.g. time off work, change in status), and any significant out-of-pocket subject expenses (e.g. medications, travel, parking). These resources will be based on patient specific data collected alongside the quality of life portion of the study. Health system and societal resources will be quantified over the course of the trial to generate utilization information by patients in each study arm, which will be valued with health system unit costs (e.g. formularies, public sources) and societal unit costs (e.g. income). We will generate an average cost per study subject by treatment arm to estimate an overall mean cost per study arm.

If the efficacy results are different between the two treatment arms, we will conduct a cost effectiveness analysis, evaluating both incremental costs and clinical outcomes (e.g., survival). If there is no significant clinical benefit, we anticipate that there will be differences in QOL between the two treatment arms and will conduct a cost-utility analysis. This cost-utility analysis will estimate the quality adjusted life years (QALY) gained from treatment with ipatasertib and fulvestrant compared to fulvestrant alone. This will be determined by combining the health preference value of each health state and the time frame in which one experiences that health state in both study arms. Health preferences will be measured with the EQ-5D-5L, which is a well-used and standardized measure of health status for economic analyses (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf). The EQ-5D-5L will be collected alongside the study QOL instrument.

The budget impact of introducing ipatasertib will be estimated by assessing the cost per patient and the number of patients per year.

Sensitivity analyses will be conducted on the estimated costs and benefit to test the robustness of the incremental ratios calculated.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Hoffman La-Roche Ltd. may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with the economic outcomes, the first author will generally be the Health Economics Coordinator on the trial committee.
- In the event of a separate paper dealing with the correlative studies outcomes, the first author will generally be the Correlative Sciences Chair on the trial committee.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

14.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by, the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, language, linguistic proficiency, age, religion, race, national or ethnic origin, colour, disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

15.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from the subject (i.e. the pregnant female) should not be collected from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information from them. If the main consent form adequately addresses the pregnancy notification and collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG. CCTG also considers the main consent form signed by the trial participant adequate consent for notification and collection of the outcome of a pregnancy of a trial participant's pregnant partner. Any information collected from the trial participant's pregnant partner can only be collected following their informed consent.

A trial-specific consent form for "Pregnancy Follow-up" can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Exposure Reporting

Information from and/or about the subject (i.e. the exposed individual) should not be collected from and/or about them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about and/or from them.

A trial-specific consent form for "Exposure Follow-up" can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the exposed individual).

Participants will not be withdrawn from the main trial as a result of a refusal or withdrawal of permission to provide information related to the exposure.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an "Exposure Follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

This trial is registrational and will be conducted under the intensive monitoring program. CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

Participating centres may be subject to an inspection by regulatory authorities and audits by CCTG, Hoffman-La Roche Ltd. or by the Group responsible for oversight of participating centres. Audits may only be conducted after consultation with CCTG.

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Distribution for Canadian sites

Details of drug distribution, supply and control/accountability are provided in the MA.40 Pharmacy Information Manual available on the MA.40 trial website.

Ipatasertib/placebo and fulvestrant are supplied by Roche to the CCTG distributor Bay Area Research Logistics (BARL) and will be distributed by BARL to participating sites in Canada.

A start up supply of ipatasertib/placebo and fulvestrant will be distributed to the activated site following receipt of confirmation from CCTG that all essential documents required for study activation have been submitted by the participating site to the CCTG office. Sites should allow for 5 working days for drug shipments to arrive.

Investigational product should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label.

Resupply

For re-supply of fulvestrant, sites should submit a Request for Drug Shipment Form (available on the MA.40 website). This form should be submitted directly to BARL as per the instructions provided on the form. Once received, BARL will process the request and initiate shipment of re-supply. Sites should allow for 5 working days for shipment to arrive.

Ipatasertib/placebo stock will be re-supplied automatically as treatment kits are used.

Drug Accountability

The investigational products are to be prescribed only by the Qualified Investigator or Sub-investigators having this delegated duty on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained, accounting for the receipt, dispensation, return and/or destruction of the investigational product utilizing the Drug Accountability Log, available on the MA.40 trial website. At the end of the study, it must be possible to reconcile shipment records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for and documented.

Drug Destruction

Drug Destruction of Patient Returns

Unused trial medication returned by the patient may be destroyed per local policy, AFTER accountability and reconciliation has been completed by the monitor and a drug destruction log has been issued. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

Drug Destruction of Expired Medication

The CCTG Study Coordinator must be contacted prior to destruction of expired medication to ensure an extension of expiry date is not expected. Expired trial medication may be destroyed per local policy, AFTER accountability and reconciliation has been completed by the monitor and a drug destruction log has been issued. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

Drug Destruction of Unused Medication (End of Trial)

Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure. At the end of the study, it must be possible to reconcile delivery records with records of usage/returned stock by completion of the study drug accountability forms. Any discrepancies must be accounted for. At the end of the study, after the monitor has completed drug accountability, a copy of the drug accountability forms and drug destruction forms will be kept with the centre files.

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED
ONLY FOR PATIENTS ENROLLED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy and appropriate storage is available. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of enrollment.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except quality of life and health utility questionnaires. Quality of Life and Health Economics Questionnaires will be completed on paper by the patient and the answers will be entered into the EDC system by centre staff.

For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the MA.40 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation *	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Patient Registration	Prior to registration (for stratification)	At the time of registration (for stratification)	• Consent forms** • Diagnostic pathology report, including ER and HER2 result • Baseline radiology reports (e.g. CT/MRI chest/abdomen/pelvis, bone scan) and/or clinical photographs of skin lesions (if applicable) • Tumour Measurement Worksheet • Foundation Medicine genomic alteration report from post-registration analysis	• ECG report • Radiology report or clinical evidence of progression on prior CDK 4/6 inhibitor + AI
Patient Enrollment	Prior to enrollment	At the time of patient enrollment/assignment to treatment		
Baseline Report	At the time of enrollment	Within 2 weeks after enrollment		
Correlative Studies Report (Tumour, Blood, Digital Images)	Continuous running-log folder	Update prior to each shipment of tumour and blood samples. Prior to each upload of digital images****		
Concomitant Medications Report	Continuous running log folder			
Treatment Report	Each cycle of treatment	Within 2 weeks after completion of each cycle	*When applicable:* Radiology reports from each disease assessment (CT/MRI chest/abdomen/pelvis, bone scan), and/or clinical photographs of skin lesions (if applicable), Tumour Measurement Worksheet, Patient Oral Drug Administration Diary, Home Blood Glucose Diary (if applicable)	• ECG report
End of Treatment Report	At the time of **permanent** discontinuation of protocol treatment.	Within 2 weeks after permanent discontinuation of protocol treatment		
Relapse/Progression Report	At the time of objective disease progression	Within 2 weeks of knowledge of progression		

Table continues on next page …

Electronic Folder	Required at	To be completed electronically	Supporting Documentation *	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Follow-up Report	At each follow up visit prior to disease progression	Within 2 weeks after visit	Radiology reports from each disease assessment (CT/MRI chest/abdomen/pelvis, bone scan), and/or clinical photographs of skin lesions (if applicable), Tumour Measurement Worksheet, Home Blood Glucose Diary (if applicable)	• ECG report
Short Follow-up Report	At each follow-up visit after disease progression	Within 2 weeks after visit	Home Blood Glucose Diary (if applicable)	• ECG report
Death Report	At the time of patient death	Within 2 weeks after knowledge of death	*When applicable:* Autopsy/post-mortem report/hospital discharge summary	
Withdrawal of Consent	At the time patient has withdrawn consent to participate in the clinical trial AND for further data submission	Within 2 weeks of consent withdrawal	Signed and date clinic note or letter to document patient's withdrawal of consent.	
AESI report	At the time of the event	Initial report due within 1 working day of knowledge of the event. Updated report required within 10 days of the event		All relevant test reports, admission and discharge summaries/notes and other documentation if requested
SAE Report***	At the time of the event	Initial report due within 1 working day of knowledge of the event. Updated report required within 10 days of the event		All relevant test reports, admission and discharge summaries/notes and other documentation if requested

* Scan and upload in the EDC Supporting Document Upload Tool (SDUT) – please refer to the slide set on the MA.40 web page for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and may be reflected in the Centre Performance Index (CPI) for Canadian sites. All relevant patient identifiers and any other prohibited personal information must be fully and completely blacked out on all source documentation, as per national and local privacy protection regulations and requirements. Acceptable methods include:

- **Fully opaque** sticker placed over the identifiers prior to scanning.
- Electronic black box placed over identifiers in PDF document that is subsequently printed and then scanned (NOTE: do not send the unprotected PDF file with black boxes included as these can be moved/removed easily after opening the document).
- **Fully opaque** black marker. Please ensure that the information under the marker cannot still be seen on the scanned document (often markers are translucent and the identifiers can in fact be seen after scanning).
- Electronic stripping of identifiers prior to upload

For quality assurance purposes, supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials or a two/three letter code assigned by your centre.

** Required for Canadian centres: it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact (black out) the participant's name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual.

*** See Section 9.0 Serious Adverse Event Reporting for details.

**** For details regarding DICOM image upload, please see Digital Imaging Collection Manual posted on the MA.40 web page.

The collection of the following information will ***NOT*** be done through the EDC system. Instead submit as follows:

Data	Required at	Collection /Submission	Comments
EORTC QLQ-C30 NCI PRO-CTCAE	• Baseline • Day 1 of cycles 2-4 then at the time of imaging for disease assessment beginning with the 24 week assessment • 4 week post-treatment visit • At 12 week follow-up visit if patient discontinued protocol treatment prior to PD and/or with related grade ≥ 3 toxicities • No longer required once patient has started a new anti-cancer treatment	Patient to complete on paper; site to enter data into EDC system within corresponding folders.	Retain paper questionnaires at the site.
EQ-5D-5L	• Baseline • day 1 of every other cycle beginning with cycle 3 • 24 months after enrollment • at 3, 12, 24, 36, 48 and 60 months of follow up. • No longer required once patient has started a new anti-cancer treatment	Patient to complete on paper; site to enter data into EDC system within corresponding folders.	Retain paper questionnaires at the site.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX V - QUALITY OF LIFE (AND HEALTH UTILITY) ASSESSMENT(S)

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life and health utility measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data and health utility can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

This study will use three patient-reported questionnaires:

Quality of Life:

- EORTC QLQ-C30, a widely used, cancer specific health-related quality of life questionnaire which will be used to capture the multidimensionality of quality of life in advanced breast cancer.

Adverse Events:

- PRO-CTCAE, a validated questionnaire which will provide a patient self-report of adverse events

Health Economics:

- EQ-5D-5L, a health utility instrument

Instructions for Administration of a Quality of Life Questionnaire

1. Preamble

   Quality of life and/or health utility data are collected for research purposes, and will usually not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-enrollment (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life and/or health utility questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable). If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire and/or health utility should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

   Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

   If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

   If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

   If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

   Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life and/or Health Utility Component

The only time that we will not require a patient to complete the quality of life and/or health utility questionnaires is if s/he cannot comprehend either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life and/or Health Utility Questionnaire

   If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life and/or Health Utility Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL (and/or health utility) assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **MA.40**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to enrollment (within 7 days)

During protocol treatment:

☐ Day 1 cycle 2 ☐ Day 1 cycle 3 ☐ Day 1 cycle 4 ☐ 24 week disease assessment ☐ 32 week disease assessment
☐ 40 week disease assessment ☐ _____ week disease assessment

Off Treatment:

☐ 4 weeks post-treatment

☐ week 12 follow-up

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (MA.40)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

NCI PRO-CTCAE Questionnaire – ENGLISH

CCTG Trial: **MA.40**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to enrollment (within 7 days)

During protocol treatment:

☐ Day 1 cycle 2 ☐ Day 1 cycle 3 ☐ Day 1 cycle 4 ☐ 24 week disease assessment ☐ 32 week disease assessment
☐ 40 week disease assessment ☐ _____ week disease assessment

Off Treatment:

☐ 4 weeks post-treatment

☐ week 12 follow-up

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

NCI PRO-CTCAE - MA.40

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
1a.	In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

2.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

3.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
3a.	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3b.	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

4.	In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
4a.	In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

5.	In the last 7 days, did you have any RASH?	
	☐ Yes	☐ No

6.	In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

7.	In the last 7 days, how OFTEN did you have PAIN?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐Almost constantly
7a.	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
7b.	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

8.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
8a.	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

Do you have any other symptoms that you wish to report?
☐ Yes ☐ No Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Thank you for completing this questionnaire!

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

EQ-5D-5L

Health Utilities Questionnaire – ENGLISH

CCTG Trial: **MA.40**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to enrollment (within 7 days)

During protocol treatment (required after every second cycle):

☐ Day 1 cycle 3 ☐ Day 1 cycle 5 ☐ Day 1 cycle 7 ☐ Day 1 cycle 9 ☐ Day 1 cycle _____

☐ 24 months after registration

Off Treatment – (required at 3, 12, 24, 36, 48 and 60 months of follow up):

☐ 3 months ☐ 12 months ☐ 24 months ☐ 36 months ☐ 48 months ☐ 60 months

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EQ-5D-5L Questionnaire

CCTG : MA.40

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

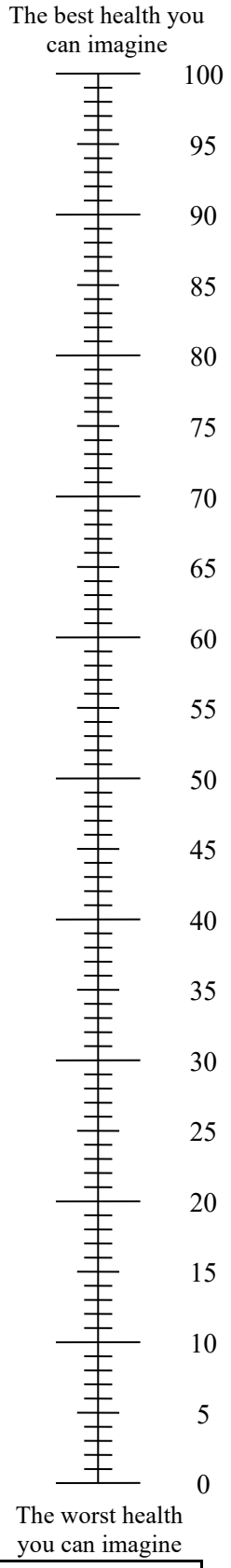
PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



YOUR HEALTH TODAY = ☐

Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VI - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX VII - EXAMPLES OF STRONG AND MODERATE CYP3A INHIBITORS AND STRONG CYP3A INDUCERS

This table is to provide examples and is not intended to be a complete list; names may vary in different locations.

Strong CYP3A inhibitors	**Moderate CYP3A inhibitors**	**Strong CYP3A inducers**
VIEKIRA PAK[1]*	erythromycin*	rifampin*
indinavir*	fluconazole*	mitotane*
tipranavir*	darunavir	avasimibe
ritonavir*	dronedarone*	rifapentine
cobicistat*	crizotinib*	apalutamide
ketoconazole*	atazanavir	phenytoin*
idelalisib*	letermovir	carbamazepine*
troleandomycin*	GSK2647544	enzalutamide*
telaprevir*	aprepitant*	St John's Wort[3]*
danoprevir*	casopitant	lumacaftor
elvitegravir*	amprenavir	rifabutin
lopinavir*	faldaprevir	phenobarbital
itraconazole*	imatinib*	
voriconazole*	verapamil*	
mibefradil	netupitant	
LCL161	nilotinib	
clarithromycin*	grapefruit juice[2]	
posaconazole*	tofisopam*	
telithromycin*	cyclosporine*	
grapefruit juice[2]	ACT-178882	
conivaptan*	ciprofloxacin*	
nefazodone*	magnolia vine *(Schisandra sphenanthera)*	
nelfinavir*	isavuconazole	
saquinavir*	cimetidine*	
ribociclib	FK1706	
diltiazem*	clotrimazole*	
boceprevir*	fluvoxamine*	

[1] VIEKIRA PAK = paritaprevir/ritonavir + ombitasvir + dasabuvir

[2] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g. high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g. low dose, single strength)

[3] The effect of St. John's wort varies widely and is preparation-dependent.

* Drugs listed in FDA website

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

This table is prepared to provide examples of clinical inhibitors and inducers of CYP3A. Data were collected based on a search of the University of Washington Drug Interaction Database

APPENDIX VIII - BLINDING / UNBLINDING

Ipatasertib and matching placebo are identical in appearance as are the bottles in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's urgent management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding (i.e. almost all urgent situations can be managed by discontinuing study drug).

If a patient is unblinded, they are considered to be off ipatasertib/placebo treatment. Therefore the need to break the blind must first be discussed and approved by the CCTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient's medical record. Treatment identification information should be kept confidential.

Please note: *Requests to unblind for information only or to permit participation in other clinical trials will not be considered until the trial has been unblinded and reported.*

Unblinding Procedure:

To unblind the treatment for a patient you must contact CCTG.

From 8am-4pm (EST): Please send an email to the Study Coordinator or Senior Investigator including the trial code, patient identification, patient initials, last treatment kit (if applicable) and the reason for the unblinding request. Once approval is obtained from the Senior Investigator, authorized personnel at CCTG will unblind the patient and send the unblinding information via email to the Investigator who requested the unblinding.

From 4pm-8am (EST) and statutory holidays: Please phone the following number as appropriate:

North America calls: 833-896-9955 Toll Free

International calls: 613-507-3861

Note that the country code for Canada is "1".

You will be required to provide basic information regarding the trial code, patient identification, last treatment kit (if applicable), and the reason for the unblinding request as well as contact information of the caller (and the Investigator/treating physician to whom the information is to be relayed if different from the caller). The unblinding information will be conveyed to the Investigator by phone and may also be followed with a confirmation email or fax.

APPENDIX IX - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.

  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Lisa Gallinaro Study Coordinator, CCTG Email: lgallinaro@ctg.queensu.ca	613-533-6430	613-533-2941
	Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Stephen Chia Study Chair Email: schia@bccancer.bc.ca	604-877-6000	604-877-6107
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator, CCTG or: Lisa Gallinaro Study Coordinator, CCTG	613-533-6430	613-533-2941
DRUG ORDERING (Canadian Sites) See Appendix II for full details.	*Fulvestrant* Manual re-supply via: Bay Area Research Logistics Email: barl@barl.ca	905-527-1938	905-527-1196
	Ipatasertib/placebo: Automatic re-supply via Mango : Lisa Gallinaro Study Coordinator, CCTG Email: lgallinaro@ctg.queensu.ca	613-533-6430	613-533-2941
REQUESTS FOR UNBLINDING	During office hours (8 am-4 pm EST): Lisa Gallinaro Study Coordinator, CCTG Email: lgallinaro@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
	After office hours (4 pm-8 am EST) and statutory holidays: North American calls (toll free): 833-896-9955 International calls: 613-507-3381 Note that the country code for Canada is "1".		