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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE Ib AND OPEN LABEL PHASE II STUDY OF CFI-402257 IN COMBINATION WITH WEEKLY PACLITAXEL IN PATIENTS WITH ADVANCED/METASTATIC HER2-NEGATIVE BREAST CANCER

CCTG Protocol Number: **IND.236**

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to University Health Network (UHN).

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 UHN and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to UHN and CCTG 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 UHN with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to UHN and CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

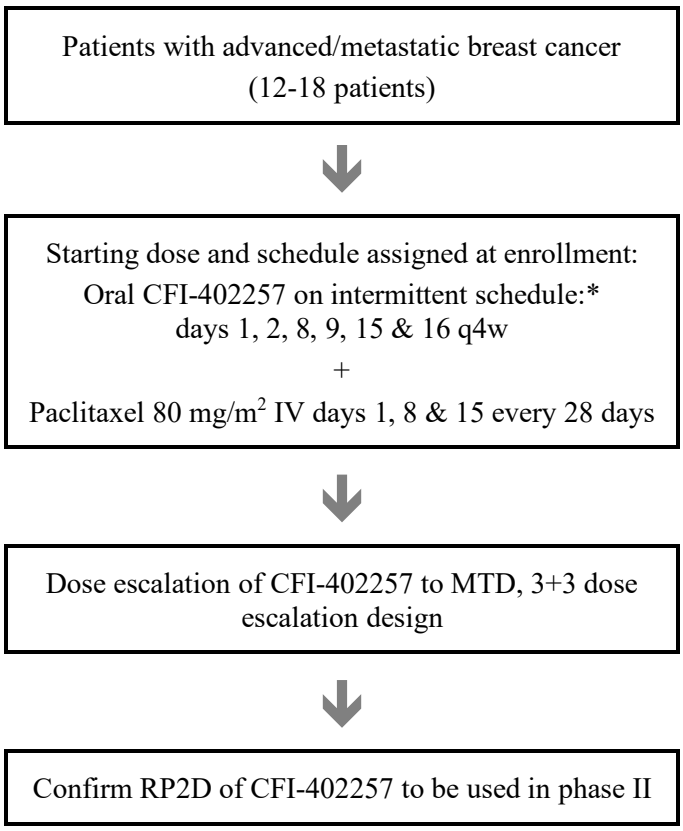
Protocol Number: CCTG IND.236

CENTRE: _____

TREATMENT SCHEMA

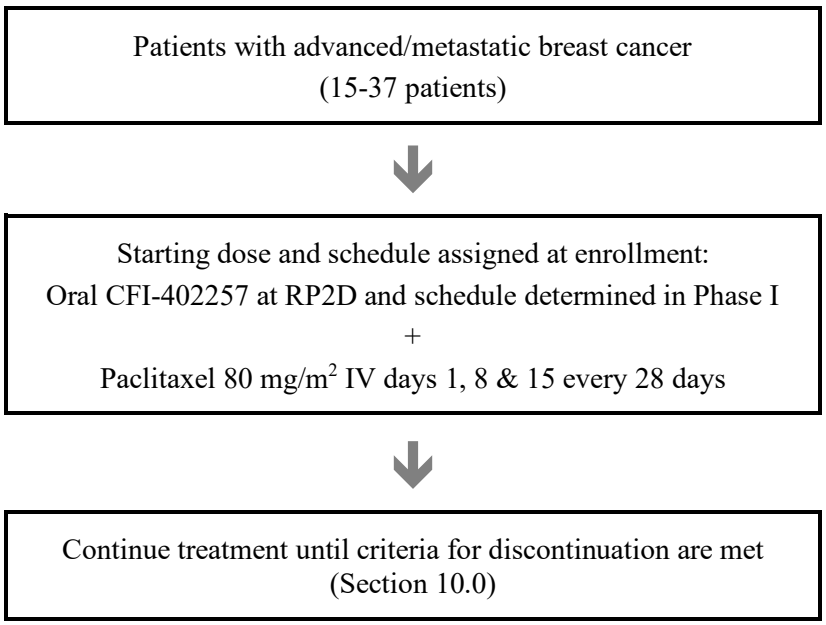
This is an open-label, multicentre, phase Ib/II study of CFI-402257 in patients with advanced/metastatic breast cancer. Approximately 12-18 patients will be enrolled in the phase Ib portion, and 15-37 patients will be enrolled in the phase II portion. This study is being conducted by the Canadian Cancer Trials Group (CCTG) and supported by a Stand Up To Cancer (SU2C) Canada – Canadian Breast Cancer Foundation Grant and Ontario Institute for Cancer Research (OICR).

Phase Ib:



* may be revised (see Section 6.3.2)

Phase II:


Patients with advanced/metastatic breast cancer
(15-37 patients)
Starting dose and schedule assigned at enrollment:
Oral CFI-402257 at RP2D and schedule determined in Phase I
+
Paclitaxel 80 mg/m2 IV days 1, 8 & 15 every 28 days
Continue treatment until criteria for discontinuation are met
(Section 10.0)

1.0 OBJECTIVES

1.1 Primary Objective

Phase I:

- To establish the safety and tolerability of CFI-402257 given orally in combination with weekly paclitaxel in a q4w schedule and to identify the recommended phase II dose (RP2D) in patients with advanced/metastatic breast cancer.

Phase II:

- To evaluate the anti-tumour activity of the CFI-402257 + paclitaxel combination when administered at the RP2D by determining the objective Overall Response Rate by RECIST 1.1 (RR, including Complete (CR) and Partial Responses (PR)).

1.2 Secondary Objectives

- To estimate the Clinical Benefit Rate (CBR, defined as CR or PR or stable disease (SD) > 16 weeks in duration).
- To evaluate the safety and tolerability of CFI-402257.
- To explore, if indicated, the pharmacokinetic profile of CFI-402257 and paclitaxel.

1.3 Exploratory Objectives

- In serial tumour biopsies, to explore evidence of a pharmacodynamic (PD) target effect (compared to published literature), and to estimate CFI-402257 levels.
- To evaluate the genomic alterations and other molecular features (e.g. gene or protein expression levels) which may be associated with response and/or clinical benefit.

2.0 BACKGROUND INFORMATION AND RATIONALE

Over the past decades, relapse rates for early stage breast cancer have declined significantly due to improvements in adjuvant systemic therapy, such as taxanes, aromatase inhibitors, and trastuzumab. However, metastatic breast cancer (MBC) remains the second most common cause of cancer-related mortality in women. Commonly used treatment options for patients who have relapsed after adjuvant therapy include hormonal therapy for patients who have hormone receptor positive tumours. Patients with receptor negative tumours, those who have organ metastases and those patients who are refractory to hormonal manipulation may be treated with systemic chemotherapy, usually with agents that they have not received as adjuvant therapy. Chemotherapy may include capecitabine, taxanes or eribulin, among others, while anthracyclines are rarely used because of prior exposure. Weekly paclitaxel is commonly used, especially in patients with prior taxane exposure, and is well tolerated *[Seidman 2001, Seidman 2008]*. Although many patients respond to cytotoxic chemotherapy, their disease is incurable and invariably progresses, usually within 6-8 months of starting treatment. New treatment approaches are needed.

TTK protein kinase (Mps1) is a recognized potential anti-cancer drug target. TTK is a dual-specificity serine-threonine kinase that is critical for the spindle assembly checkpoint (SAC), chromosome alignment and error correction in mitosis. Inhibition of TTK kinase activity causes cells to prematurely exit mitosis with unattached chromosomes, resulting in severe chromosome missegregation, aneuploidy and eventually cell death. TTK is overexpressed in 38% of all breast tumours and in 85% of triple negative/basal-like breast cancer (TNBC), which is the most genomically unstable breast cancer subtype, indicating that inhibition of TTK is a potential therapeutic strategy in this disease.

CFI-402257 is a selective and potent inhibitor of TTK (Mps1), a key kinase in maintaining genomic integrity during mitotic cell division through establishment and maintenance of the mitotic checkpoint. In vitro, CFI-402257 inhibits the growth of seven breast cancer (luminal/HER2) cell lines tested with a range 1-1250 nM (median IC_{50} of 9 nM, mean of 188 nM). The growth inhibition of five basal breast cancer cell lines tested was also observed with a range 2-30 nM) (median IC_{50} of 26 nM, mean IC_{50} of 18.4 nM). Furthermore, oral QD treatment of CFI-402257 demonstrated dose dependent monotherapy efficacy in mice with established tumours from xenografted human TNBC cells and similar results were also obtained with another TNBC xenograft. These preclinical results indicate that CFI-402257, as monotherapy, may have clinical activity in patients with breast cancer.

Paclitaxel, a chemotherapeutic agent, is a microtubule stabilizer that inhibits mitosis through the activation of the spindle assembly checkpoint (SAC) and has proven clinical efficacy in patients with advanced/metastatic breast cancer. In vivo preclinical data using TNBC-derived cell lines showed that combination of CFI-402257 and paclitaxel was tolerated with no additional toxicities and resulted in a higher rate of complete regression in 2 different cell line models. In the MDA-MB231 cell line xenograft model, while single agent treatment with either paclitaxel at 18 mg/kg/week or CFI-402257 at 25 mg/kg on a 2 days on/5 days off schedule resulted in no long term complete regressions in any animals, the combination of these two regimes induced long term complete regressions in 3 of 8 animals. Emerging preclinical data from other groups also indicate that abrogation of SAC using TTK inhibitors is synergistic with paclitaxel in tumour growth inhibition. This was, in fact, observed in a broad range of xenograft models, including those showing acquired or intrinsic paclitaxel resistance. These novel findings provide the rationale for this study, combining CFI-402257 and paclitaxel chemotherapy in patients with MBC.

This study includes a dose escalation phase to identify the recommended phase II dose (RP2D) of oral CFI-402257 when used in combination with paclitaxel 80 mg/m^2 IV days 1, 8 & 15 every 28 days, followed by a single arm phase II to evaluate the anti-tumour activity of the combination. The overall response rate will be benchmarked against a historical cohort from the recently reported IND.213 CCTG trial *[Bernstein 2018]*. In the control arm, patients (n=38) received paclitaxel 80 mg/m^2 IV days 1, 8 & 15 every 28 days and the ORR was 23.7% (all partial responses). With a median follow-up of 29.5 months, the median PFS for the control arm was 3.38 months and the median overall survival (OS) was 10.4 months. The phase II portion of this study will aim to enroll a similar patient population to IND.213.

3.0 BACKGROUND THERAPEUTIC INFORMATION

Consult the most recent version of the investigators brochure for current information.

3.1 CFI-402257 Chemical Information

CFI-402257, which has the chemical name N-cyclopropyl-4-(7-(((cis-3-hydroxy-3-methylcyclobutyl)methyl)amino)-5-(pyridin-3-yloxy)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methylbenzamide bisphosphate hemihydrate, is being developed by the University Health Network (UHN) as a new chemical entity for the treatment of cancer. This molecule was identified in the course of a focused synthetic medicinal chemistry effort directed towards the discovery of inhibitors of TTK protein kinase, also known as monopolar spindle 1 (Mps1).

The clinical drug substance of CFI-402257 is bisphosphate hemihydrate. CFI-402257 capsules are intended for oral (po) administration.

3.2 Chemical Structure

The chemical structure of CFI-402257 is shown below:

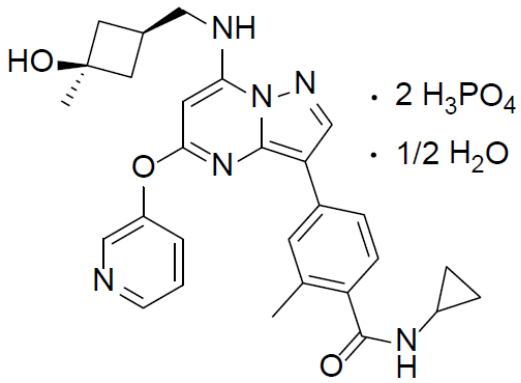


Table 1: Chemical structure and formula of CFI-402257.

Molecular Formula:	C28H30N6O3·2H3PO4·0.5H2O
Formula Weight:	703.57 (bisphosphate hemihydrate)
Molecular Weight:	498.57 (free base)
Solubility:	Water, pH 2: 26 µg/mL Water, pH 7: <1 ug/mL
Appearance:	Off-white to light yellow crystalline solid

Table 2: Nomenclature.

Chemical Name:	N-cyclopropyl-4-(7-(((cis-3-hydroxy-3-methylcyclobutyl)methyl)amino)-5-(pyridin-3-yloxy)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methylbenzamide bisphosphate hemihydrate
Chemical Class:	Pyrazolopyrimidine
CAS Registry Number:	TBD

3.3 Mechanism of Action

CFI-402257 is a selective and potent inhibitor of TTK (Mps1), a key kinase in maintaining genomic integrity during mitotic cell division through establishment and maintenance of the mitotic checkpoint. TTK is a dual-specificity serine-threonine kinase that is critical for the recruitment of spindle assembly checkpoint (SAC) proteins to unattached kinetochores, mitotic checkpoint complex (MCC) formation, and thus anaphase promoting complex/cyclosome (APC/C) inhibition. TTK is also required for chromosome alignment and error correction. Inhibition of TTK kinase activity causes cells to prematurely exit mitosis with unattached chromosomes, resulting in severe chromosome missegregation, aneuploidy and eventually cell death. TTK is overexpressed in several tumours, and higher levels correlate with worse prognosis and may contribute to the survival and proliferation of aneuploid cells. Depletion of TTK expression in cancer cells by RNA interference leads to gross chromosome segregation errors and cell death. Thus, pharmacologic inhibition of this target would be expected to produce antiproliferative and cytotoxic effects against cancer cells.

3.4 Experimental Antitumour Activity

Non-clinical pharmacology studies with CFI-402257 have been performed *in vitro* in enzyme assays, human tumour cell lines, and tumour initiating cell lines, and *in vivo* in human cancer cell line xenografts and primary tumour xenografts.

CFI-402257 is a potent and specific inhibitor of TTK (K_i = 0.09 nM, IC_{50} = 1.2 nM), with minimal activity (≤50% inhibition at 1 μM) against 265 other protein kinases. CFI-402257 has antiproliferative activity against a number of cancer cell types, and causes effects consistent with inhibition of TTK kinase activity. The molecule is a potent intracellular inhibitor of exogenous TTK autophosphorylation with an EC50 = 6.5 nM. No effect on Aurora kinase A (AURKA), Aurora kinase B (AURKB) or Histone H3 phosphorylation is observed (EC50s > 400 nM). CFI-402257 causes failure of the SAC, leading to gross aneuploidy (with minimal polyploidy) and cell death. Oral administration of CFI-402257 effectively inhibits growth in multiple murine models of human tumours, including cancer cell line xenografts and primary tumour xenografts. In these non-clinical studies, CFI-402257 demonstrates dose-dependent antitumour activity, is active when administered under a range of dosing schedules, and is well-tolerated by mice when administered at efficacious doses. Immunohistochemical analysis of sections taken from MDA-MB-231 breast cancer xenograft tumours study revealed a decrease in the percentage of phospho-histone H3 (pHH3)-positive cells with CFI-402257 treatment, consistent with inhibition of TTK *in vivo*.

CFI-402257 demonstrated a desirable combination of potent inhibition of cancer cell growth *in vitro* and significant exposure upon oral dosing in mice, rats and dogs. Robust, dose-dependent suppression of tumour growth was achieved upon oral dosing in a number of xenograft models with minimal effects on mouse body weight and other parameters of toxicity.

3.5 Animal Toxicology

The potential toxicity of CFI-402257 was investigated in a genetic toxicity study (bacterial Ames reverse mutation assay), two multiple dose tolerability studies, and two multiple dose toxicity and toxicokinetics (TK) studies. An oral route of exposure for the *in vivo* preclinical studies was used which is the clinical route of administration, and the studies were conducted using rodent (rat) and non-rodent (dog) species.

In both rats and dogs, the primary targets were the hematopoietic system and the gastrointestinal tract. The effects in the hematopoietic system included depression of WBC lineages and reticulocytes which correlated with hypocellularity of the bone marrow. Although increases in RBC mass cell parameters were compatible with hemoconcentration secondary to dehydration, the CFI-402257-related decreases of reticulocytes in rats and dogs could potentially translate into anemia with longer treatment duration. Decreases in circulating and resident lymphocytes in lymphoid tissues may have been a direct effect of compound administration, secondary to stress, or a combination of both factors. Changes supporting an increase in endogenous corticosteroids (stress) included adrenal cortical hyperplasia and increased glucose levels in some animals.

The gastrointestinal tract effects were consistent between species, involving all segments, and minimal to marked in severity with cecum most severely affected. Clinical effects in animals included loose or liquid, hemorrhagic, or otherwise abnormal stool. The gastroenteropathy was characterized by necrosis of epithelium, crypts, or glands with erosions or ulcerations, and regenerative/reparative changes including increased mitoses, cellular atypia piling up of cells, and villous fusion. In the 28-day GLP rat toxicity study, the highest non-severely toxic dose was 5 mg/kg/day. In the 28-day GLP dog toxicity study, the highest non-severely toxic dose and the no observable adverse effect level were 1.0 mg/kg/day. Both the gastrointestinal tract effects and the hematological changes were reversed upon cessation of dosing or a reduction in dose level.

A safety pharmacology study conducted in freely moving telemetrized female beagle dogs showed that treatment with CFI-402257 at doses up to 2.25 mg/kg had no adverse effects on cardiovascular or respiratory systems.

3.6 Clinical Trials

The first in human dose escalation phase I trial with CFI-402257 (CL-001) is currently ongoing (NCT02792465). As of 13 November 2020, a total of 55 subjects with various solid malignancies have been evaluated with unformulated CFI-402257 bisphosphate hemihydrate powder-in-capsule in 28-day continuous cycles ranging from 5 to 294 mg/day. 54 (98%) subjects experienced at least one treatment-emergent adverse event (TEAE). The most common adverse events (AEs) by preferred term (PT) were fatigue (50.9%), nausea (38.2%), and diarrhea (34.5%). The majority of AEs were either mild (21.8%) or moderate (36.4%). A total of 34 (61.8%) subjects reported at least one AE considered by the investigator to be related to study drug. There were 26 treatment-emergent serious adverse events (SAEs) in 16 (29%) subjects, 9 of which were considered by the investigator to be related to study drug. There were 17 deaths in total. Most were due to disease progression.

3.7 Pharmacokinetic Studies

Absorption:
In pre-clinical studies, the bioavailability of CFI-402257 was determined to be 53% in rats and 114% in dogs. The pharmacokinetics of CFI-402257 after a single oral dose was characterized by a moderate to rapid rate of absorption with a T_{max} generally of 30 minutes to 1 hour. The elimination half-life of the compound following oral administration averaged between 2.25 and 3.2 hours in mice, 2.0 and 4.6 hours in rats, and 1.5 and 5.5 hours in dogs. Repeated dose toxicokinetics studies indicated dose dependent increases in systemic exposure over the tested dose range in rats and dogs.

PK data from the current ongoing first in human Phase I study of CFI-402257 showed that there was linear dose dependent increase in C_{max} in the 6 dose escalating cohorts that had been cleared. At 56 mg oral daily dosing (N=4), which is the proposed starting dose of CFI-402257 in Phase Ib part of this study, average C_{max} was 261 ng/ml (range 45-496), AUC_{0-24} was 2621 ng.h/ml (range 575-4783), and $t_{1/2}$ was 11.3 hours (range 8.3-16.2). T_{max} was reached within 2 hours of administration.

Distribution:
CFI-402257 was 92% bound to plasma proteins in human plasma, 95% in mouse, 95% in rat, and 94% in dog plasma.

Metabolism:
At high concentrations, CFI-402257 inhibits the activity of cytochrome P450 isoenzymes CYP2C8 and CYP3A4, which metabolize paclitaxel. CFI-402257 also inhibits the activity of paclitaxel transporters OATP1B3, BCRP and PGP. Therefore, there is some potential for drug-drug interactions between CFI-402257 and paclitaxel. This potential drug-drug interaction will be investigated in the Phase II part of this study using a sparse PK sampling strategy.

Elimination:
Preliminary results from experiments in rats indicate that the primary route of excretion is in feces.

3.8 Pharmaceutical Data

Supplied:
CFI-402257 is currently supplied as a 2.5 mg, 14 mg, and a 42 mg capsule. The actual capsule strength used in this study will depend on the single agent RP2D. Doses are based on the active moiety alone.

Bottles are induction sealed and capped with 38 mm child-resistant closures. Bottles are appropriately labeled to reflect drug product strength, contents, and recommended storage condition. Capsules should be swallowed whole. CFI-402257 is to be taken on an empty stomach. Patient should avoid food for 2 hours before taking CFI-402257 and 1 hour after taking CFI-402257.

Stability:
Stability studies indicate the drug product is stable for at least three months when not refrigerated. Shipments to site pharmacies will be temperature controlled and monitored. Refrigeration or temperature monitoring is not required for Patient transport of study drug to and from the clinic.

Storage:
Storage facilities and clinical site pharmacies should store CFI-402257 capsules at refrigerated temperature (2-8 °C). Patients should store capsules at ambient temperature.

Route of Administration:
Oral.

3.9 Paclitaxel

Paclitaxel is not supplied for this study as it is commercially available and will be sourced from the Canadian market. Centres should consult the manufacturer's guidelines for further details.

In brief, paclitaxel has extensive extravascular distribution and/or tissue binding. Paclitaxel is metabolized by cytochrome P450 isoenzymes CYP2C8 (primarily) and CYP3A4, and caution should be exercised when administering paclitaxel with known substrates, inducers or inhibitors of these isoenzymes.

4.0 STUDY POPULATION

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of enrollment. Questions about eligibility criteria should be addressed prior to enrollment.

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. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

4.1.1 Patients must have histologically and/or cytologically confirmed diagnosis of breast cancer that is advanced/metastatic/recurrent or unresectable, for which no curative therapy exists, and for which systemic therapy is indicated. Only female patients will be enrolled.

4.1.2 All patients must have a formalin fixed paraffin embedded tissue block (from primary or metastatic tumour) available and must have provided informed consent for the release of the block.

Biopsies are optional but strongly encouraged for patients with accessible disease suitable for biopsy. The timing of tumour biopsies for patients who provide informed consent and are willing is prior to treatment (after enrollment) and again no later than the end of the day following the day 8 paclitaxel infusion. Lesions planned for biopsy may not be the only target lesion.

4.1.3 Presence of clinically and/or radiologically documented disease. All radiology studies must be performed within 21 days prior to enrollment (within 28 days if negative).

For phase Ib, patients are not required to have measurable disease as defined by RECIST 1.1 but must not have bone-only or marker only disease.

For phase II, all patients must have measurable disease as defined by RECIST 1.1. The criteria for defining measurable disease are as follows:

Chest x-ray	$\geq$ 20 mm	
CT scan (with slice thickness of 5 mm)	$\geq$ 10 mm	→ longest diameter
Physical exam (using calipers)	$\geq$ 10 mm	
Lymph nodes by CT scan	$\geq$ 15 mm	→ measured in short axis

4.1.4 Patients must be $\geq$ 18 years of age.

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

4.1.6 Patients must be able to swallow oral medications.

4.1.7 *Previous Therapy*

Chemotherapy:
Patients must have received at least one non-taxane containing chemotherapy regimen for advanced or metastatic disease unless:

a) they have relapsed within 6 months of completion of adjuvant/neoadjuvant chemotherapy AND the regimen did not contain taxane, or;

b) they have received taxane and/or anthracycline containing adjuvant/neoadjuvant chemotherapy 6 or more months prior to relapse, **or**;

c) they have a documented contraindication to palliative chemotherapy other than weekly paclitaxel.

Patients must **not** be considered appropriate for endocrine therapy and must not have received taxanes in the metastatic setting.

Other Systemic Therapy:
Patients may have received other therapies including endocrine therapy, immunotherapy, and/or targeted therapies (including CDK4/6 inhibitors).

Patient may NOT have had previous exposure to any therapy within the pharmacological class (TTK/MPS1 inhibitor).

Patients must have recovered (to at least grade 0 or 1) from all reversible toxicity other than alopecia related to prior chemotherapy or systemic therapy and have adequate washout as follows:

Longest of one of the following:

- Two weeks,
- 5 half-lives for investigational agents,
- Standard cycle length of standard therapies (e.g. at least 3 weeks for capecitabine).

Radiation:
Prior external beam radiation is permitted provided a minimum of 28 days (4 weeks) 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.

Surgery:
Previous surgery is permitted provided that a minimum of 21 days (3 weeks) have elapsed between any major surgery and date of enrollment, and wound healing has occurred.

4.1.8 *Laboratory Requirements*
(must be done within 7 days prior to enrollment)

Hematology	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
Chemistry	Bilirubin	≤ 1.0 x ULN (upper limit of normal)*
	AST and ALT	≤ 3.0 x ULN ≤ 5.0 x ULN if patient has liver metastases
	Serum creatinine *or*: Creatinine clearance**	≤ 1.5 x ULN ≥ 60 mL/min

* If confirmed Gilbert's, eligible provided ≤ 3 x ULN.

** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:
Females: GFR = 1.04 x (140-age) x weight in kg / serum creatinine in μmol/L

4.1.9 Women of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. 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 a 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/she is responsible for beginning contraceptive measures.

Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (failure rate of < 1% per year) while on study and for 6 months after the last dose of CFI-402257. Cessation of birth control after this point should be discussed with a responsible physician. See Section 9.3 for additional details.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include 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 will be considered eligible if an ultrasound is negative for pregnancy.

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

4.1.11 Patients must be accessible for treatment and follow-up. Patients registered 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 registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.

4.1.12 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 history of other untreated malignancies or malignancies which required therapy within the past 2 years. Patients with other malignancies of a nature that do not require treatment may be eligible after consultation with the CCTG.

4.2.2 Patients with HER2 positive breast cancer.

4.2.3 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.

4.2.4 Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects). Patients with a significant cardiac history, even if controlled, should have a LVEF $\geq$ 50%.

4.2.5 Patients are not eligible if they have a known hypersensitivity to the study drug(s) or their components.

4.2.6 Patients with history of central nervous system metastases or spinal cord compression unless have received definitive treatment, are clinically stable and do not require corticosteroids.

4.2.7 Patients who have contraindications to treatment with paclitaxel and/or neuropathy > grade 1. *(Please contact CCTG if any questions about the interpretation of this criterion.)*

4.2.8 Concurrent treatment with other investigational drugs or anti-cancer therapy.

4.2.9 Pregnant or breast feeding women.

4.2.10 Prohibited medications as listed in Appendix V Table 1. Patients being treated with drugs listed in Appendix V Table 2 may be enrolled, but should be monitored carefully for toxicities resulting from potential interactions between CFI-402257 and these drugs. In addition, patients must avoid consumption of the fruit or juice of Seville oranges (e.g. marmalade), grapefruit, pomelos and star fruit from 7 days before the first dose of study drug and during the entire study due to potential CYP3A4 interaction with the study drug. Regular orange juice is allowed.

4.2.11 Patients with any medical condition that could impair the administration of oral agents including significant bowel resection, inflammatory bowel disease or uncontrolled nausea or vomiting.

4.2.12 Patients treated with full dose warfarin. Patients with history of deep vein thrombosis or pulmonary embolus who are being treated with therapeutic doses of low molecular weight heparin, direct factor Xa inhibitors or prophylactic dose anticoagulants may be enrolled.

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	Pre-study (≤ 7 days prior to enrollment)	Within 21 days prior to enrollment	Weekly, and as clinically indicated	Day 1 each cycle, and as clinically indicated	Every 8 weeks for 3 assessments then every 12 weeks	4 weeks after end of last cycle date	3 monthly follow-up (only required for pts without confirmed PD and ongoing toxicities[1]) then every 6 months until death
History and Physical Exam*							
Including: height and weight, ECOG performance status, documentation of all measurable and non-measurable disease, clinical tumour measurements (if applicable); Vital signs: blood pressure, heart rate, temperature	X			X		X	
Laboratory Procedures/Assessments*							
CBC (neutrophils, lymphocytes, hemoglobin, platelets)	X		X[2]			X[4]	X[4]
PTT, PT/INR	X			X			
Serum creatinine[3], electrolytes (calcium, potassium, magnesium) bilirubin, ALP, AST, ALT, LDH, albumin, glucose	X		X[2]	X		X[4]	X[4]
Pregnancy Test[5]	X			X[6]			
Urinalysis	X[7]						
Radiology							
Tumour Imaging (Chest/upper abdomen CT scan; bone scan[8]; other scans as necessary to document disease)		X[9,10]			X[11]	X[11]	X[11]
Other Investigations							
EKG	X			X			
LVEF	X[12]			As clinically indicated			
Archival Tumour Tissue	X[13]						
Correlative Studies and PK Blood Collection (plasma and serum)	X[14]		See Section 12.0 for details				
Tumour biopsies	X[15]		X[15]				
Patient Drug Administration Diary (CFI-402257)		Each Cycle					
Adverse events	X		Continuously			X[1]	

footnotes on following page ...

*	Pre-treatment blood draws and physical exams may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). 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.
1	Adverse events felt to be related to protocol therapy will be followed until resolved to ≤ Grade 2. Irreversible events may not need to be followed. Contact CCTG to discuss. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) (see Appendix IV).
2	CBC prior to each planned paclitaxel dose (all cycles); biochemistry weekly for cycles 1 and 2 (which also includes week 4 in cycle 1 and 2), more frequently if clinically indicated. Patients with grade 3 or 4 thrombocytopenia, febrile neutropenia, grade 3 or 4 neutropenia or grade 3 or 4 biochemical drug related toxicity must have CBC/biochemistry at least alternate days until recovery to ≤ Grade 2 (consult CCTG if biochemistry is not felt to be drug related toxicity).
3	If creatinine > 1.5 x ULN, calculated CrCl is required and must meet eligibility criteria for re-treatment.
4	Required at 4 weeks. To be done additionally every 3 months thereafter to follow abnormal lab results felt related until resolved to ≤ Grade 2.
5	For women of childbearing potential only (urine or serum test). Within 72 hours prior to enrollment. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
6	Only required as clinically indicated in WOCBP.
7	Required at baseline then as clinically indicated.
8	Bone scan is required at baseline for all patients. Thereafter, bone scan is only required to be repeated if positive at baseline to confirm CR, PR or SD, and/or PD is suspected and as clinically indicated.
9	To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule every 8 or 12 weeks even if cycles are delayed.
10	28 days if negative.
11	To be done additionally every three months thereafter until relapse or progression for patients with CR, PR, SD response.
12	Only if significant cardiac history (see Section 4.2.4) and then as clinically indicated.
13	Must be confirmed available prior to enrollment on ALL patients. See Section 12.0 for details.
14	After enrollment but before the first dose of study treatment.
15	Optional paired biopsies should be obtained after enrollment but prior to first dose and again no later than the end of the day following the day 8 paclitaxel infusion (must be done the day of the day 8 paclitaxel infusion or no later than the following day). Contact CCTG if unable to schedule within this time period.) See Section 12.1 for details.

5.1 Follow-up for Ineligible Patients

The follow-up requirements for patients who have received no protocol therapy include submission of the Baseline Report and the Off Treatment Report. Data submission for all other participants who have received at least one dose of protocol therapy should follow the protocol to allow for treatment and adverse event assessment, irrespective of eligibility status.

6.0 ENTRY/ENROLLMENT PROCEDURES

6.1 Entry Procedures

All 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 patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.236 trial specific web-site. If sites experience difficulties accessing the system and/or registering patients, please contact the help desk (link in EDC) or the IND.236 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 following information will be required:

- trial code (CCTG IND.236)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- optional consent version date
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- height and weight

6.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2, the actual surface area or 2.2 may be used. CCTG BSA calculations are based on the Mosteller formula.

6.3 Phase I

In the dose escalation part of the study, patients will be treated with oral doses of CFI-402257 on an intermittent schedule (planned as 2 days on, 5 days off) in combination with weekly intravenous paclitaxel as below. One cycle is defined as 28 days.

Each Cycle	Week 1							Week 2							Week 3							Week 4						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
CFI-402257	X	X						X	X						X	X												
Paclitaxel	X							X							X													

On cycle days 1, 8, 15 where both drugs are administered, CFI-402257 is to be taken prior to and within 60 minutes of the start of paclitaxel infusion. For patients undergoing PK sampling, CFI-402257 is to be taken immediately prior to (within 5 minutes) the start of the paclitaxel infusion.

6.3.1 *Justification for Starting Dose and Schedule*

In a parallel phase I study being conducted by the University Health Network, oral doses of up to 168 mg single agent CFI-402257 have been tolerated when given on a continuous daily schedule (1/6 DLT (Grade 3 ANC)). Please refer to Section 3.0 and the investigator brochure for most up to date information.

In this study, we plan to test the highest tolerable continuous dose of CFI-402257 as determined by the most recent data of the single agent phase I study, on an intermittent schedule (2 days weekly x 3 q28 days) in combination with weekly paclitaxel at a planned dosage of 80 mg/m^2.

6.3.2 *Dose Escalation*

Dose escalation of CFI-402257 will occur in a standard 3+3 design. Dosing is 'flat' and not by weight or BSA. Dose cohorts will initially include a minimum of 3-4 patients. If no DLTs are observed in the first 3 evaluable patients, CFI-402257 dose escalation will proceed according to the dose escalation schema below. If 1 patient out of 3 experiences a dose limiting toxicity (DLT), up to 3 additional patients will be recruited at that dose level (for a maximum of 6). If only 1 out of 6 patients in that dose level experiences a DLT, escalation to the next level will occur. If 2 out of 3, or 2 out of 6 patients experience DLT at dose level 1, the dose will be de-escalated as shown in the table below. If 2 out of 3, or 2 out of 6, patients experience DLT at other dose levels, no further dose escalation will occur. For the first dose level, the first patient will be followed for at least 7 days before the next patient is enrolled.

Toxicity will be evaluated according to the CTEP Active Version of the CTCAE (See Appendix IV). Dose escalation decisions will be made after review of the data from the current dose level by the CCTG and investigators.

If the first dose level of CFI-402257 is not tolerable, dose level -1 may be used. The planned starting dose may be adjusted if data from ongoing studies suggest that a higher or lower dose would be appropriate. Intermediate dose levels, other than those defined below, may be determined by the CCTG and investigators following a review of the data from this trial and other emergent data. If appropriate, based on review of clinical or pharmacokinetic data, an intermediate schedule (for example, 3 days on and 4 days off) will be tested. No intra-patient dose escalation will occur.

A. Planned Starting Dose Levels

Dose level	CFI-402257 (mg) Dose on Days 1, 2, 8, 9, 15 & 16 (every 28 days)
DL-1	42
Starting Dose (DL1)*	56
DL2	84
DL3	126
DL4	168

table continues on next page ...

B. Subsequent Dose Levels

Subsequent Dose Levels			
Worst grade* toxicity in previous dose level			% increase in dose of CFI-402577 from previous dose level
Hematologic	Non-hematologic	DLT?	
2	1	no DLT	50%
3	2	no DLT	30-49%
Follow DLT definition below		≤ 1 DLT of 6 pts	0-29%
		2 DLT of 3/6 pts	0%
* Considered related to CFI-402257. Actual doses will be dependent on this table and capsule size. If required, schedule may also be modified (i.e. number of days dosed per week).			

Paclitaxel will not be dose escalated. No intra-patient dose escalation will occur. The planned starting dose of paclitaxel may be de-escalated if drug-drug interaction occur and safety data suggest that a lower dose would be appropriate.

6.3.3 *Dose Limiting Toxicity, Maximum Tolerated Dose and Recommended Phase II Dose*

Dose Limiting Toxicity:
Dose limiting toxicity (DLT) will be defined as any of the following related (to either drug) adverse events occurring during cycle 1:

Hematologic Toxicity:
- Grade 3 or 4 neutropenia complicated by fever ≥ 38.3°C or infection,
- Grade 4 neutropenia of ≥ 7 days duration,
- Grade 3 thrombocytopenia complicated by bleeding,
- Grade 4 thrombocytopenia of any duration.

Non-Hematologic Toxicity:
- Grade 3 or 4 non-hematologic toxicity (excluding inadequately managed nausea and vomiting, alopecia or grade 3 fatigue lasting < 7 days).
- Other toxicities of concern to the investigators and CCTG including the omission of 2 doses of paclitaxel or toxicities requiring > 21 days delay in next cycle and or late toxicities.

Maximum Tolerated Dose:
The maximum tolerated dose (MTD) will be determined, and will be defined as the dose level at which < 1/6 patients experience a dose limiting toxicity (DLT; defined below) during cycle 1.

Recommended Phase II Dose (RP2D):
The recommended phase II dose will be determined prior to proceeding to the phase II study, based on the observed MTD in cycle 1, with additional consideration of tolerability in subsequent cycles beyond the DLT period.

6.3.4 *Replacement of Patients*

If a patient is not evaluable for toxicity for Cycle 1, that patient may be replaced to ensure the minimum number of patients are evaluable. Patients must receive ≥ 75% planned dose of CFI-402257 and paclitaxel to be considered evaluable for toxicity, unless the study drug/s was held or discontinued for CFI-402257 or paclitaxel-related toxicity and/or DLT has occurred.

6.4 Phase II

In the single arm phase II part, the RP2D of the CFI-402257+paclitaxel combination will be evaluated.

6.5 Study Enrollment

Enrollment will be provided electronically.

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, should an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All 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 enrollment.

All 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 patients who don't receive treatment are outlined in Section 5.1.

6.6 Inclusion of Women and Minorities

This trial will only enroll women. Men are excluded because the historical comparison cohort used to benchmark the response rate from this study included only one male patient. There are no exclusions based on race or ethnicity in this trial. This study, however, will be presented to patients through the major cancer-treatment institutions of the Canadian provinces, to which all racial/ethnic groups have equal access. The intention, therefore, is to recruit subjects from racial/ethnic groups in close approximation to the incidence of the disease in these groups.

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*

Agent	Dose	Route	Duration	Schedule
CFI-402257	See Section 6	Oral	-	Days 1, 2, 8, 9, 15, 16 q4w*
Paclitaxel	80 mg/m^2	IV	1 hour	Days 1, 8, 15 q4w
* May be modified based on data from Phase 1 component.				

One cycle will be defined as 4 weeks. On days when both CFI-402257 and paclitaxel are administered, oral CFI-402257 should be taken prior to paclitaxel infusion (see Section 6.3 for timing).

7.1.2 *Premedication*

All patients will receive prophylactic dexamethasone, diphenhydramine and ranitidine as per standard centre practice prior to each paclitaxel infusion.

The suggested premedication regimen is: dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and ranitidine 50 mg IV all given 30 minutes before paclitaxel infusion.

7.1.3 *Dose Modifications*

Doses will be held or reduced for hematologic and other 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) (see Appendix IV). The use of an institution's written standard procedures for dose modifications of paclitaxel is permitted. Dose reductions or treatment interruption for reasons other than those described below may be made by the clinical investigator if it is deemed in the best interest of patient safety. Whenever possible, these decisions should first be discussed with the senior investigator. Note: response evaluation must be performed every 8 weeks even if cycles are delayed. Centres should follow local policy regarding dose modifications based on changes in weight.

The major toxic effects which may limit paclitaxel dose are cytopenias, arthralgia and/or myalgia, and peripheral neuropathy.

The most common CFI-402257 adverse event was nausea in thirteen subjects (23.6%). Other events include myelosuppression (including neutropenia and anemia) and febrile neutropenia, diarrhea, infection (including typhlitis and colitis), mucosal inflammation and stomatitis, vomiting, decreased appetite, dry mouth, dysgeusia, dyspepsia, alopecia, flushing/hot flush, headaches, fatigue, arthralgia, myalgia, pruritus and rash. 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.

The next cycle should not be given until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L and resolution of all drug related toxicity to $\leq$ grade 2. Contact CCTG if clinically appropriate exceptions are indicated. Note: growth factors may not be used to maintain dosing (see 7.2.1).

If paclitaxel is held or delayed, CFI-402257 should be held or delayed to maintain the concurrent dosing schedule. Doses reduced for toxicity will not be re-escalated. Omitted doses will not be replaced (if day 8 is not given, it will be considered omitted for that cycle, and day 15 will be given on time (if appropriate).

Patients who discontinue paclitaxel for toxicity may continue receiving CFI-402257, at the discretion of the investigator, providing that the patient has no evidence of disease progression.

Specific details of dose adjustments are listed below.

Table 1. Guidelines for CFI-402257 and Paclitaxel Dose Modifications for Treatment Related Adverse Events at D1, D8 and D15 of each treatment cycle.

Dose on Day 1 of cycle

On D1, paclitaxel and CFI-402257 should not be given until ANC $\geq$ 1.0 x 10^9/L and platelets $\geq$ 100 x 10^9/L, and all other toxicity $\leq$ grade 2.

Worst toxicity in previous cycle	Management/Action for paclitaxel and CFI-402557
HEMATOLOGIC	
2 consecutive omissions for hematologic toxicity (including delay of Day 1 $\geq$ 7 days)	1st occurrence: Reduce paclitaxel by 1 DL 2nd occurrence: Reduce CFI-402257 by 1 DL
Febrile neutropenia or thrombocytopenic bleeding	Reduce paclitaxel and CFI-402257 by 1 DL
Grade 4 thrombocytopenia	
Grade 4 neutropenia $\geq$ 7 days	
NON-HEMATOLOGIC	
Grade $\geq$ 2 myalgia and/or arthralgia	Consider NSAIDS, acetaminophen and, if not relieved, prednisone or gabapentin, according to local standard of care. If persistent and intolerable, reduce paclitaxel by 1 DL.
Grade 2 and 3 motor or sensory neuropathy	Reduce paclitaxel by 1 DL (if not already reduced at D8 or D15 in previous cycle)
Other grade 3	Reduce the causal drug by 1 DL (if not already reduced at D8 or D15 in previous cycle)
Other grade 4	Discontinue

- For grade 3-4 hematologic/biochemistry toxicity, repeat CBC and biochemistry alternate days until recovered to $\leq$ grade 2.
- If the treatment-related toxicity is not resolved within 21 days, the patient will be removed from the study, except in the case of patients benefiting from treatment, in whom treatment may be resumed following interruptions of > 21 days upon resolution of toxicity to baseline or Grade 1, after discussion with CCTG.
- Two DL reductions are permitted for paclitaxel and CFI 402257 before discontinuation.

Dose on Day 8 or 15 of Cycle

On D8 and D15, paclitaxel and CFI-402257 should not be given until ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L, and all other toxicity has resolved to ≤ grade 2.

Worst toxicity on Day 8 or 15	Management/Action for paclitaxel **and** CFI-402557
HEMATOLOGIC	
Grade 3 and 4 ANC	Omit both and follow table above
Grade 2 and 3 platelets	Omit both and follow table above
Grade 4 platelets or thrombocytopenic bleeding	Omit both and follow table above
NON-HEMATOLOGIC	
Grade ≥ 2 myalgia and/or arthralgia	Consider NSAIDS, acetaminophen and, if not relieved, prednisone or gabapentin according to local standard of care. If persistent, reduce paclitaxel by 1 DL.
Grade 2 and 3 motor or sensory neuropathy	Omit both and then reduce only paclitaxel by 1 DL
Other grade 3	Omit both and then reduce the causal drug by 1 DL
Other grade 4	Discontinue

- For grade 3-4 thrombocytopenia, febrile neutropenia, grade 3 or 4 neutropenia or grade 3 or 4 biochemical drug related toxicity, repeat CBC and biochemistries on alternate days until recovered to ≤ grade 2. (Consult CCTG if biochemistry is not felt to be drug related toxicity).Two DL reductions are permitted for paclitaxel and CFI-402257 before discontinuation.
- If the treatment-related toxicity is not resolved within 21 days, the patient will be removed from the study (except in the case of patients benefiting from treatment, in whom treatment may be resumed following interruptions of > 21 days upon resolution of toxicity to baseline or Grade 1, after discussion with CCTG.

Table 2: Dose Reductions for CFI-402257. (See Table A. Section 6.3.2)

Initial Dose*	**1st Reduction**	**2nd Reduction**	**3rd Reduction**
56 mg	42 mg	28 mg	DISCONTINUE
84 mg	56 mg	42 mg	DISCONTINUE
126 mg (range 112-126)	84 mg	56 mg	DISCONTINUE
168 mg (range 140-168)	126 mg	84 mg	DISCONTINUE
Higher doses	Reduce by 1 DL	Reduce by 1 DL	DISCONTINUE

* For intermediate doses (or higher doses) not listed, calculate dose reductions using ranges listed under initial dose column or contact CCTG.

Table 3: Dose Reductions for Paclitaxel.

Initial Dose	**1st Reduction**	**2nd Reduction**	**3rd Reduction**
80 mg/m2	65 mg/m2	50 mg/m2	DISCONTINUE

Paclitaxel Hypersensitivity Reaction

Severity	Action
Mild (e.g. mild flushing, rash, pruritus)	Attempt to complete the infusion under close supervision.
Moderate (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	• Stop the paclitaxel infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV. • Once symptoms have resolved, resume paclitaxel infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.
Severe (e.g. one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	• Stop the paclitaxel infusion; give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators if indicated. • Do not rechallenge with paclitaxel

If hypersensitivity reactions occur, pre-medications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV pre-medications given 30 minutes prior to paclitaxel: dexamethasone 10 mg, diphenhydramine 25 mg, and H2-antagonist (e.g. ranitidine 50 mg). If no hypersensitivity reactions occur, standard pre-medications (see above) will be used for subsequent paclitaxel doses. Contact CCTG in advance if responding patients have severe hypersensitivity reactions and treating investigator feels a switch to standard nab-paclitaxel is indicated.

Paclitaxel Renal and Hepatic Dysfunction

Follow product monograph/local policies for hepatic and renal dysfunction dose modifications.

7.1.4 *Duration of Therapy*

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 10.0). Patients who discontinue paclitaxel for toxicity may continue receiving CFI-402257 at the discretion of the investigator.

7.1.5 *Patient Compliance*

Treatment compliance will be monitored by drug accountability, as well as recording drug administration in the patient's medical record and case report form (CRF).

7.2 Concomitant Therapy

7.2.1 *Permitted*

- Other supportive and palliative care (e.g. pain control) as required throughout the study.
- Bone-targeted therapy for patients with bone metastases (bisphosphonates or denosumab)
- Anti-emetics or anti-diarrheal agents as required.
- Growth factors may be used according to centre policy to treat life threatening toxicity but cannot be used in place of protocol defined dose adjustments or prophylactically. Please consult CCTG in the case of patients experiencing multiple delays/omissions as exceptions may be made for patients who are benefitting from protocol therapy.

7.2.2 *Not Permitted*

- Administration of any other anti-cancer or investigational therapy is not permitted while the patient is receiving protocol therapy. Thereafter, patients may be treated at the investigator's discretion.
- Concurrent radiation treatment (Note: if patients require palliative radiation or prophylactic radiation (e.g. of brain) consult CCTG for exception to this rule; protocol therapy will need to be held prior to and during the radiation.)
- Patients should avoid the ingestion of large amounts of grapefruit and Seville oranges (and other products containing these fruits (e.g. grapefruit juice or marmalade).
- Prohibited medications as listed in Appendix V Table 1. Drugs listed in Appendix V Table 2 may be used, but patients should be monitored carefully for toxicities resulting from potential interactions between CFI-402257 and these drugs.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 *Evaluable for Response*

All 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]*.

8.2 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.

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*

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 < 10 mm 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. Confirmation of response is only required in non-randomized studies.

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. Confirmation of response is only required in non-randomized studies.

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 has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. 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 deterioration". 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.

For non randomized trials, where confirmation of response is required, best overall response can be interpreted as follows:

Response: First Time Point	Subsequent Time Point	BEST Overall Response	Also Requires
CR	CR	CR	Tumour nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

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 start of treatment 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 ≥ 10 mm 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 (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded 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.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, regardless of whether they are unexpected or related to protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late serious adverse event occurring after this 30-day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 9.2 for reporting instructions).
- 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 IND.236 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 7 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:

Linda Hagerman
IND.236 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

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 IND.236 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) who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.9.

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants. Pregnancies occurring up to 6 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy 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 pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant participants (if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ 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 in a timely manner, 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 for a duration of 30 days. 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 (613-533-2812/ 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.

9.4 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 causal relationship with protocol treatment cannot be ruled out).

9.5 CCTG Reporting Responsibility to UHN

UHN will be notified of all reportable serious adverse events within 1 working day of receipt by CCTG.

9.6 UHN Reporting Responsibilities

UHN shall notify CCTG of individual safety reports from other studies using CFI-402257, which may affect the overall safety profile of the study and which they have reported to Health Canada. In addition, UHN will provide 3 monthly line listings to CCTG for all other reports.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial IND.236 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial IND.236 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.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

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.
- Completion of therapy as outlined in Section 10.2. Efforts should 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 Duration of Protocol Treatment

(see Section 8.0 for response definition)

- Treatment with CFI-402257 will continue until progression
- Treatment with paclitaxel will continue to the maximum number of cycles permitted per local practice or until progression in the absence of unacceptable toxicity (see Section 7).
- Patients who progress will go off study at the time progression is documented clinically and/or radiographically.
- If CFI-402257 is discontinued for toxicity, paclitaxel should be continued according to standard clinical practice off protocol.
- If paclitaxel is discontinued for toxicity, CFI-402257 may be continued in patients with no evidence of disease progression. No other anticancer therapy may be co-administered. If patients require other anti-cancer therapy, then CFI-402257 must be discontinued.

10.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months until relapse (see Section 5.0 for investigations to be performed). Continued follow up after progression (on treatment or during follow up), using an abbreviated form (including subsequent therapies) every 6 months is required until CCTG advises centres that the final analysis has been performed and follow up can be discontinued. Death report will be required on all patients unless advised by CCTG. Due within 2 weeks of knowledge of death (see Appendix III - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the IND.236 trial specific website, which will include details regarding sample preparation, handling and shipping.

Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of enrollment to the trial, the surgical/ histology number and/or patient initials. 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

Planned testing for hereditary genetic defects predisposing to malignant disease will not be carried out.

As all biomarker testing done for this study will be conducted in a research laboratory, the results are not validated. There are no plans to return results to patients.

12.1 Protocol-Mandated Correlative Studies

Tumour Tissue Collection - Archival

The submission of a representative block of the diagnostic tumour tissue is mandatory for participation in this trial**.** One tumour block and one adjacent normal tissue block are requested from all of the biopsies or resections of the breast tumour.

If no primary cancer blocks are available, one block of metastatic tissue can be sent alone. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to enrollment of the first patient to allow cores (two 2 mm cores of tumour from the block) and a predetermined number of slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request.

Tumour Tissue Collection (serial paired samples)
Biopsies are optional but strongly encouraged for patients with accessible disease suitable for biopsy. Optional biopsies may be performed at baseline (after enrollment, prior to treatment) and again no later than the end of the day following the day 8 paclitaxel infusion (must be done the day of the day 8 paclitaxel infusion or no later than the following day). Please contact CCTG if unable to schedule within this time period.

Blood Collection
The submission of samples at baseline and after 4 cycles (or at off treatment) for cfDNA is also mandatory for participation in this trial. Samples will be collected to measure dynamic changes in levels of tumour-derived DNA in plasma with study treatment.

Planned Assays on Tissue

Molecular analyses including but not limited to next-generation DNA sequencing and immunohistochemistry will be performed on archival and fresh tumour (or normal tissue) materials to identify potential biomarkers of response, including TTK, pKNL1, expression of APC/C components, etc.

Drug levels will also be measured to evaluate distribution of CFI-402257 to tumour.

12.2 Pharmacokinetic Studies

Clinical pharmacokinetic studies are a required component of study participation and will be performed in all patients where required by the protocol, in accordance with the sampling schedule detailed in the Pharmacokinetic Manual.

Blood samples for paclitaxel must be collected from the arm opposite to the infusion line. If a heparin lock is used, a minimum of 1 mL of whole blood should be withdrawn and discarded prior to each collection to ensure that the heparin does not contaminate the specimen. 5 ml venous blood samples will be collected into EDTA anticoagulant containing tubes.

Exact infusion start and stop times and as well as infusion parameters (concentration of dose solution, total volume delivered, and flow rate settings) for each dose corresponding to pharmacokinetic sampling, will be recorded on the Pharmacokinetics Form. If for any reason a sample is not collected, the sample date and time should be recorded as not done (ND) on the Pharmacokinetics Form. All samples are to be taken at the times specified. If samples are taken at times different from this schedule, they are still valuable provided the time is accurately recorded. Inaccurately recorded times may hinder the investigation. Changes to the PK sampling schedule may occur as emergent clinical data become available. Blood samples for PK will be collected as follows:

- In phase I dose escalation, at dose/exposure levels of CFI-402257 that exceed those characterized as the RP2D in the phase I First in Human monotherapy study, PK sampling will be performed on C1D1 (for CFI-402257 only).
- In phase II, PK sampling for both agents will be performed on C2D8 (if unable to sample on day 8 then C2D15 is permissible after discussion with CCTG) in the first 10 patients enrolled. Assays on these samples will only be performed if clinically indicated (for example, a PK interaction is suspected based on clinical data).

In each case, CFI-402257 is to be administered immediately prior to the start of the paclitaxel 1 hr infusion, and samples collected at the following times:

Phase I

On Cycle 1, Day 1: Pre-dose CFI-402257, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 24 hours

Cycle and Day	Time in Relation to CFI-402257 Administration
C1D1	Pre-dose of CFI-402257
	1 hour post administration
	2 hours post administration
	4 hours post administration
	6 hours post administration
	8 hours post administration
C1D2	24 hours post administration* (collect sample prior to CFI-402257 dosing)
*strongly recommended	

Phase II:

On Cycle 2, Day 8: Pre-dose CFI-402257 and paclitaxel, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours and 24 hours after CFI-402257 and paclitaxel administration, and pre-CFI-402257 and paclitaxel administration on Day 15.

Cycle and Day	Time	Time in Relation to Paclitaxel Infusion
C2D8	0	Pre-dose (of BOTH CFI-402257 and paclitaxel)
	30 min	30 minutes after beginning of paclitaxel infusion
	60 min	End of paclitaxel infusion
	2 hours	1 hour post end of paclitaxel infusion
	3 hours	2 hours post end of paclitaxel infusion
	4 hours	3 hours post end of paclitaxel infusion
	6 hours	5 hours post end of paclitaxel infusion
	8 hours	7 hours post end of paclitaxel infusion
C2D9		24 hours post end of paclitaxel infusion (and prior to CFI-402257 dosing)
C2D15		Pre-dose (of BOTH CFI-402257 and paclitaxel)

Note: if PK sampling is done on Day 15 then the last sample is taken on day 22.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is an open label multicentre phase Ib trial to establish the safety and tolerability of CFI-402257 given orally in combination with weekly paclitaxel in a q4w schedule and to identify the recommended phase II dose (RP2D) in patients with advanced/metastatic breast cancer. The phase Ib part will utilize a 3+3 design. The phase II part will evaluate the anti-tumour activity of the CFI-402257 and paclitaxel combination when administered at the RP2D by determining the objective Overall Response Rate by RECIST 1.1.

13.2 Primary Endpoints and Analysis

Phase Ib: the primary endpoint is toxicity and establishing the RP2D of the combination of CFI-402257 with weekly paclitaxel in a q4w schedule.

Phase II: the primary endpoint of this part is objective response rate, defined as the proportion of response evaluable patients who had complete response (CR) or partial response (PR) as their best response as assessed by RECIST 1.1 criteria (i.e. a 30% decrease in the sum of the longest diameters of the target lesions maintained for at least 4 weeks (CR), or complete disappearance of disease and cancer related symptoms, also maintained for at least 4 weeks (CR)). The exact 95% confidence interval for the response rate will be calculated. The median and range of the duration of response, defined as the time from date of CR or PR to the date when progression or death is observed, will be estimated based on Kaplan-Meier method.

Secondary objectives include Clinical Benefit Rate (CBR, defined as CR or PR or stable disease (SD) > 16 weeks in duration).

13.3 Sample Size and Duration of Study

Final sample size will be dependent upon the number of dose levels required to reach the RP2D. We anticipate recruiting between 12 to 18 patients in the phase Ib.

For phase II, a 2-stage Simon design will be used. The overall response rate is benchmarked against a historical cohort from the recently reported IND.213 CCTG trial *[Bernstein 2018]*. In the control arm, patients (n=38) received paclitaxel 80 mg/m^2 IV days 1, 8 & 15 every 28 days and the ORR was 23.7% (all partial responses).

Stage 1 of Accrual:
17 response evaluable patients will be entered in the first stage. Using response hypotheses of $H_0 \leq$ 20% and $H_a \geq$ 40%, we would reject the drug at the end of the first stage of accrual if 3 or less responses are seen. Otherwise, an additional 20 patients will be accrued to the cohort.

Stage 2 of Accrual:
An additional 20 response evaluable patients will be accrued. We would accept the combination as active if 11 or more responses are observed.

Significance Level and Power:
The procedure described above tests the null hypothesis (H0) that the response rate is 20% versus alternating hypotheses (H1) that the response rate is 40%. The significance level (i.e. the probability of rejecting H0 when it is true) is α=0.10 and the power (i.e. the probability of rejecting H0, i.e. deciding the regimen is active, when H1 is true) is 0.90.

13.4 Safety Monitoring

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

13.5 Pharmacokinetics

Pharmacokinetic samples will be taken as indicated in Section 12.2 but assays will only be performed if indicated. Comparisons will be made between the different dose levels of CFI-402257 for pharmacokinetic analysis. Plasma levels of paclitaxel will also be measured at specific time points defined as above to characterize paclitaxel pharmacokinetics when administered in combination with CFI-402257. ANOVA and linear regression or comparable nonparametric statistical methods will be used to make dose group comparisons. Pharmacokinetic analyses using noncompartmental analysis will be conducted. Pharmacokinetic analyses may include plasma AUC, T½, Tmax, Cmax, Cmin, and Cavg.

13.6 Correlative Studies

Tumour biopsies will be collected prior to initiation of study treatment and again no later than the end of the day following the day 8 paclitaxel infusion in up to 15 patients to determine any evidence of target effects. Results will be compared to those published in literature *[Zasadil 2014]*. Circulating tumour DNA analysis will also be performed to measure dynamic change in levels of tumour derived circulating DNA in plasma with study treatment. These analyses are exploratory but will be analyzed using appropriate statistical tests.

Molecular analysis including but not limited to next-generation DNA sequencing and immunohistochemistry will be performed on archival and fresh tumour materials to identify potential biomarkers of response. Evaluation of the association between genomic alterations, and other molecular features (i.e. gene or protein expression levels), and evidence of benefit, will be considered exploratory, and associations will be analyzed in a descriptive manner.

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 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.

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). Research supported by a Stand Up to Cancer Canada - Canadian Breast Cancer Foundation Breast Cancer Dream Team Research Funding, with supplemental support of the Ontario Institute for Cancer Research through funding provided by the Government of Ontario (Funding Award Number: SU2C-AACR-DT-18-15). Stand Up to Cancer Canada is a program of the Entertainment Industry Foundation Canada. Research funding is administered by the American Association for Cancer Research International - Canada, the scientific partner of SU2C Canada.

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 study closure the manuscript has not been submitted, 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, religion, race, national or ethnic origin, colour, mental or physical 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 Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or 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 about or from them. If the main consent form adequately addresses the 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.

Trial-specific consent form for "Exposure Follow-up" can be found on the trial webpage. The appropriate 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 refusing or withdrawing permission to provide information related to the pregnancy*/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 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.

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

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.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

16.0 REFERENCES

Bernstein V, Ellard SL, Dent SF, Tu D, Mates M, Dhesy-Thind SK, Panasci L, Gelmon KA, Salim M, Song X, Clemons M, Ksienski D, Verma S, Simmons C, Lui H, Chi K, Feilotter H, Hagerman LJ, Seymour L. A randomized phase II study of weekly paclitaxel with or without pelareorep in patients with metastatic breast cancer: final analysis of Canadian Cancer Trials Group IND.213 Breast Cancer Research and Treatment: 167 (2): 485 - 493, 2018

Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline version 1.1. Eur J Can 45: 228-47, 2009.

Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, Gipson G, Burstein H, Lake D, Shapiro CL, Ungaro P, Norton L, Winer E, Hudis C. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. Apr 1;26(10):1642-9, 2008.

Seidman AD, Fornier MN, Esteva FJ, Tan L, Kaptain S, Bach A, Panageas KS, Arroyo C, Valero V, Currie V, Gilewski T, Theodoulou M, Moynahan ME, Moasser M, Sklarin N, Dickler M, D'Andrea G, Cristofanilli M, Rivera E, Hortobagyi GN, Norton L, Hudis CA. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol. May 15;19(10):2587-95, 2001.

Zasadil LM, Andersen KA, Yeum D, Rocque GB, Wilke LG, Tevaarwerk AJ, Raines RT, Burkard ME, Weaver BA. Cytotoxicity of Paclitaxel in Breast Cancer is due to Chromosome Missegregation on Multipolar Spindles. Science Translational Medicine, Vol. 6 Issue 229, 229ra43, 2014.

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

General

Details of Drug Distribution, Supply and Control/Accountability are provided in the IND.236 Pharmacy Information Manual, available on the IND.236 website: (http://www.ctg.queensu.ca/trials/.html).

Distribution

Paclitaxel is commercially available and sourced from the Canadian market.

CFI-402257 will be supplied to the CCTG distributor, Bay Area Research Logistics (BARL) and distributed by BARL to participating sites in Canada.

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

A start up supply of CFI-402257 will be distributed to the activated site by BARL 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. BARL will ship CFI-402257 directly to the site pharmacy. Sites should allow for 5-7 working days for drug shipments to arrive.

Resupply

For re-supply of CFI-402257, sites should print off and submit a Drug Re-Supply Form available on the IND.236 website. This form should be submitted directly to the Study Coordinator, Linda Hagerman, at lhagerman@ctg.queensu.ca. Once received, request will be sent to BARL and BARL will process and initiate shipment of re-supply. Sites should allow for 5-7 working days for shipment to arrive.

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 IND.236 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 and documented by the site. 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 and documented by the site and approved by CCTG. 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.

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED
ONLY FOR PATIENTS REGISTERED 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 and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the IND.236 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are:

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool*	
		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.
BASELINE REPORT	Due within 2 weeks of patient enrollment.	Copies of signature pages of main and optional consent forms; relevant pathology & radiology reports.	ECG, LVEF
TREATMENT REPORT	To be completed every 4 weeks (i.e. after each cycle). Due within 2 weeks of end of course. This report documents treatment, adverse events, investigations and response assessment for each course.	Relevant radiology reports.	Patient Diary (CFI-402257).
CORRELATIVE STUDIES	See Section 12.		
END OF TREATMENT REPORT	To be completed when patient goes off protocol treatment. Due within 2 weeks of end of protocol treatment.		
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after going off protocol treatment. Due within 2 weeks after contact with patient.	Relevant radiology reports.	
FOLLOW-UP REPORT	To be completed every 3 months or 6 months (see Sections 5.0 and 10.4). Due within 2 weeks after contact with patient.	Relevant radiology reports.	
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.	

table continues on next page …

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool*	
		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.
DEATH REPORT**	Required for all patients unless advised by CCTG. Due within 2 weeks of knowledge of death.	Autopsy report, if done.	
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 9.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.		All relevant test reports, admission, discharge summaries/notes and other documentation.

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. All supporting documents must have personal identifiers redacted.

** NB It is the investigator's responsibility to investigate & report the date/cause of death of any patient who dies during this period. Any death that occurs during this protocol therapy or within 30 days after last dose must also be reported as a Serious Adverse Event as described in Section 9.0.

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 - PROHIBITED MEDICATIONS

Table 1. Drugs to be excluded

Alfentanil	Pimozide
Cyclosporine	Quinidine
Digoxin	Sirolimus
Dihydroergotamine	Tacrolimus
Ergotamine	Warfarin
Fentanyl	

Table 2. Substrates of BCRP, OATP1B1, OCT1, OCT2 and MATE. To be used with caution.

Acyclovir	Everolimus	Quetiapine
Amantadine	Felodipine	Rifampin
Aprepitant	Fexofenadine	Ritonavir
Atorvastatin	Fluticasone	Rosuvastatin
Budesonide	Ganciclovir	Saquinavir
Buspirone	Indinavir	Sildenafil
Cimetidine	Lopinavir	Simvastatin
Colchicine	Lovastatin	Sulfasalazine
Conivaptan	Lurasidone	Telmisartan
Darifenacin	Maraviroc	Thyroxine
Darunavir	Memantine	Tiprinavir
Dasatinib	Metformin	Tolvaptan
Desipramine	Midazolam	Triazolam
Dofetilide	Nisoldipine	Valsartan
Dronedarone	Olmesartan	Vardenafil
Eletriptan	Pitavastatin	
Eplerenone	Pravastatin	

APPENDIX VI - 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 a 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

PATIENT ENROLLMENT

All patients must be enrolled with CCTG before any treatment is given.

	Contact	Tel. #	Fax #
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*	613-533-6430	613-533-2411
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Linda Hagerman Study Coordinator, CCTG Email: lhagerman@ctg.queensu.ca *or:* Dr. Pierre-Olivier Gaudreau Senior Investigator, CCTG Email: p-ogaudreau@ctg.queensu.ca *or:* Dr. Lesley Seymour Director, CCTG Investigational New Drug Program Email: lseymour@ctg.queensu.ca		
STUDY CO-CHAIRS	Dr. Philippe Bedard Study Co-Chair *or:* Dr. Mihaela Mates Study Co-Chair	Contact CCTG	Contact CCTG
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Linda Hagerman Study Coordinator, CCTG Email: lhagerman@ctg.queensu.ca *or:* Dr. Pierre-Olivier Gaudreau Senior Investigator, CCTG Email: p-ogaudreau@ctg.queensu.ca *or:* Dr. Lesley Seymour Director, CCTG Investigational New Drug Program Email: lseymour@ctg.queensu.ca	613-533-6430	613-533-2411
DRUG ORDERING See Appendix II for full details.	See Appendix II and trial website: http://www.ctg.queensu.ca		