PROTOCOL DATE: 2015-NOV-09
CCTG TRIAL: MA.38

HEALTH CANADA SUBMISSION

ADMINISTRATIVE UPDATE #1: 2017-JUL-05

CANADIAN CANCER TRIALS GROUP (CCTG)

RANDOMIZED PHASE II STUDY COMPARING TWO DIFFERENT SCHEDULES OF PALBOCICLIB PLUS SECOND LINE ENDOCRINE THERAPY IN WOMEN WITH ESTROGEN RECEPTOR POSITIVE, HER2 NEGATIVE ADVANCED/METASTATIC BREAST CANCER (PALESTRA)

CCTG Protocol Number: **MA.38**

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SUPPORTED BY:	Pfizer

(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to CCTG and Pfizer.

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, 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 and Pfizer 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 Pfizer and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Pfizer and CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment 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 Pfizer with or without cause.

I understand that Pfizer requires, as a condition of providing its product, Palbociclib (the “Pfizer Product”) for this study, the following license and option with respect to any invention or discovery, whether patentable or not, made by an investigator that results from the conduct of the Study and that encompasses treatment with, or the delivery, combination, manufacture, form, formulation, or the use of, the Pfizer Product (including use in combination with other products or agents), or that is or relates to a biomarker useful in selecting patients for treatment with the Pfizer Product (a Product-Related Invention”):

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I agree as an investigator to grant the above described non-exclusive license and option to Pfizer as required.

I agree to use the Pfizer Product only as specified in the protocol. If I use, or permit others to use, the Pfizer Product for any research not authorized by the protocol ("Unauthorized Research") I acknowledge that Pfizer will be the exclusive owner of the result of that research, including any inventions or discoveries that arise out of it, whether patentable or not (collectively the "Unauthorized Inventions") and I will assign to Pfizer all interest in such Unauthorized Inventions and will cooperate with Pfizer to ensure execution and delivery of all documentation that Pfizer reasonably deems necessary to perfect Pfizer's rights in the Unauthorized Inventions.

I understand that any inventions or discoveries that are not a Product-Related Invention and/or Unauthorized Inventions will be owned by the inventors. For any inventions or discoveries that may be jointly made by CCTG, investigator and/or Pfizer, the inventions or discoveries will be jointly owned and each joint owner will retain its right to practice and exploit its undivided interested in any such invention or discovery without the consent of and without accounting to its co-owners.

Any supplemental information that may be added to this document is also confidential and proprietary to Pfizer 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 MA.38

CENTRE: _____

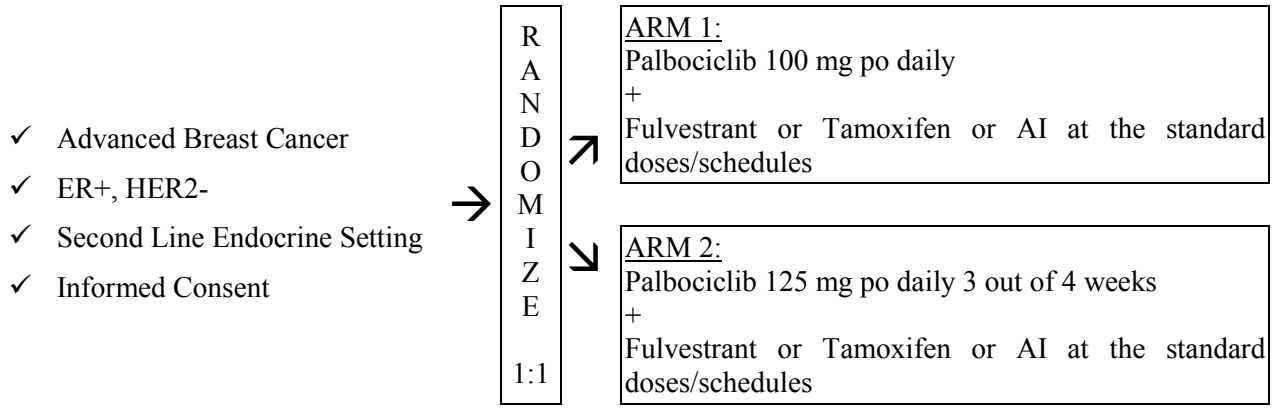
TREATMENT SCHEMA

Population

Women with documented evidence of estrogen receptor positive, HER2 negative, advanced/metastatic breast cancer, after failure of prior endocrine therapy

Stratification

- Centre
- Visceral metastases: yes versus no
- Duration of exposure to most recent endocrine therapy prior to randomization: ≥ 6 months versus < 6 months in the advanced/metastatic setting or ≥ 24 months versus < 24 months in adjuvant setting
- Planned use of Fulvestrant versus Tamoxifen versus Aromatase Inhibitor (AI)



Planned sample size: 180

Endpoints

Primary:

- Progression Free Survival

Secondary:

- Safety and Tolerability
- Response Rate (in patients with measurable disease)
- Duration of Response
- Clinical Benefit Rate
- Overall Survival

Tertiary/Exploratory:

- Patient Reported Quality of Life using EORTC QLQ-C30 and trial specific checklist
- Predictive biomarker assessment from tissue and blood sample collection
- A biorepository of tissues for future correlative studies

1.0 OBJECTIVES

1.1 Primary Objective

To compare the progression-free survival of two different dose regimens of palbociclib in combination with endocrine therapy (fulvestrant or tamoxifen or AI) as second line therapy in women with ER positive, HER2 negative, advanced/metastatic breast cancer

1.2 Secondary Objectives

To evaluate and compare between the two treatment arms with respect to:

- Safety and Tolerability
- Response Rate (in patients with measurable disease)
- Duration of Response
- Clinical Benefit Rate
- Overall Survival

1.3 Tertiary/Exploratory Objectives

To explore:

- Patient Reported Quality of Life using EORTC QLQ-C30 and trial specific checklist
- Predictive biomarker assessment from tissue and blood sample collection
- A biorepository of tissues for future correlative studies

2.0 BACKGROUND INFORMATION AND RATIONALE

Although reliable identification of steroid receptors and the introduction of tamoxifen and aromatase inhibitors resulted in major improvements in outcomes for patients with breast cancer, many patients will eventually relapse or progress due to the development of resistance to endocrine therapy. In the advanced disease setting, occurrence of resistance results in lower response rates and shorter durations of progression free survival (PFS) with every further line of palliative endocrine therapy *[Bergh 2012; Chia 2008; Howell, 2002]*. Resistance may be attributed to a shift from estrogen-dependent tumour growth to the activation of alternate growth factor signaling pathways and growth signal activation despite the absence of estrogen.

Cell cycle progression from G1 to S phase requires a complex of cyclin-dependent kinase (CDK) 4 and 6 (CDK6) and D cyclins (CCND1-3) to phosphorylate retinoblastoma (Rb). In malignant cells, genetic changes, including CCND1 amplification common in breast cancer, can result in loss of controlled cell cycle progression through G1, rendering CDK4/6 inhibition an attractive biological approach *[Osbourne 2005]*. Palbociclib is an orally available CDK inhibitor with potential antineoplastic activity. Palbociclib selectively inhibits CDK4 and CDK6 inhibiting Rb protein phosphorylation early in the G1 phase leading to cell cycle arrest *[Caldon2006; Dean 2012; Finn 2009]*. This suppresses DNA replication and decreases tumour cell proliferation.

Clinical trials of palbociclib have shown impressive clinical activity without undue toxicity. Phase I data testing a 3 weekly out of 4 dosing schedule (dose range (25-150 mg daily) identified 125 mg as the recommended phase two dose (RPTD) *[Flaherty 2012]*. Uncomplicated grade 3 or 4 neutropenia was the dose limiting toxicity (DLT). Pivotal phase II data from Finn et al (PALOMA 1) was derived from a study comparing palbociclib 125 mg orally daily 3 out of 4 weeks plus daily letrozole 2.5 mg to single agent letrozole *[Finn 2014]*. The primary endpoint was PFS. Two cohorts were enrolled based on biomarker status [ER+, HER2– (cohort 1) and ER +, HER2- plus amplification of cyclin D1, loss of p16 or both (cohort 2)]. An unplanned interim analysis of cohort 1 led to closure of cohort 2 and combination of both cohorts for the PFS analysis. Median PFS for the combined group was 10.2 months for the letrozole arm compared to 20.2 months for the combined arm (HR 0.488 95% CI 0.319-0.748; one sided p=0.0004). Grade 3/4 neutropenia was seen in 54% of 83 patients enrolled in the combined arm versus 1% Of 77 in the letrozole group. No cases of febrile neutropenia or neutropenia related infections were reported in the study. Based on these results, the US FDA granted accelerated approval to palbociclib (IBRANCE, Pfizer, Inc.) on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with ER+, HER2-, advanced breast cancer as initial endocrine-based therapy for their metastatic disease. Mature results for efficacy and toxicity were presented at the 2017 American Society of Clinical Oncology Annual Meeting. Median PFS was improved in all subgroups in the combination treatment arm compared to letrozole. Adverse events were manageable including in those patients with visceral disease. As of December 2016, there were 116 OS events. Median OS was 37.5 mos (95% CI: 31.4, 47.8) with P+L vs 34.5 mos (95% CI: 27.4, 42.6) for L (HR = 0.897 [95% CI: 0.623, 1.294]; p= 0.281)

The efficacy of palbociclib plus letrozole was confirmed in the phase III setting (PALOMA 2) *[Finn 2016]*. Combination therapy improved PFS compared to letrozole: HR for progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001. The median PFS for the palbociclib plus letrozole treated group was 24.8 months (95% confidence interval [CI], 22.1 to not estimable) versus 14.5 months (95% CI, 12.9 to 17.1) in the letrozole treated group. Adverse events were anticipated based on previous clinical data. The most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib-letrozole group vs. 1.4% in the placebo-letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%).

The phase III PALOMA-3 study compared fulvestrant plus palbociclib versus fulvestrant plus placebo *[Turner 2015]*. A preplanned interim analysis demonstrated a significantly longer PFS (primary endpoint) favoring the combination arm: investigator assessed median PFS 9.2 months versus 3.8 months HR 0.42, 95% CI, 0.32 to 0.56; P<0.001). The most common grade 3 or 4 adverse events (regardless of causality) were hematological and more frequent in the palbociclib plus fulvestrant arm versus fulvestrant arm alone including: leukopenia (25.5% versus 0.6%), neutropenia (62.0%, vs. 0.65), anemia (2.6% vs. 1.7%) and thrombocytopenia (2.3% vs. 0%). Notably, the incidence of febrile neutropenia was the same (0.6%) in both arms although there were numerically more infections in the combination arm, mostly low grade (34.2 versus 24.4%). Dose reductions occurred in more patients treated with palbociclib (31.6%) than with placebo (1.7%). Rates of discontinuation due to adverse events were numerically low in both arms but higher in patients receiving palbociclib (2.6% compared to 1.7% respectively). Subset analysis showed comparable benefit in premenopausal versus postmenopausal women (P = 0.94 for interaction between drug assignment and menopausal status). The final analysis was recently reported *[Cristofanilli 2016]*. The HR for progression free survival was o.46 (95% CI 0.36-0.59, p< 0.001). Biomarker analyses failed to demonstrate predictive roles for PIK3A status or hormone receptor expression level on response. Overall survival data is in progress. An in depth safety analysis was performed *[Verma 2016]*, No new safety signals were seen and the rate of febrile neutropenia with palbociclib expsosure was < 1%. Palbociclib associated neutropenia was effectively managed by dose reductions or delays and without any apparent impact on disease outcome.

There is accumulating experience with combination therapy palbociclib and tamoxifen. The effect of multiple dosing of tamoxifen (60 mg QD for 4 days followed by 20 mg QD for 23 days), on the single-dose PK of palbociclib (125 mg), was evaluated in 25 healthy fasted subjects in Study A5481026. Administration of palbociclib in the presence of tamoxifen and its metabolites (4-hydroxy-tamoxifen, N-desmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen) at steady state showed that palbociclib exposure was comparable with that when palbociclib was given alone. The ratios (90% CIs) of the adjusted geometric means of palbociclib AUCinf and Cmax were 108% (104%-111%) and 116% (105%-129%), respectively, following administration of palbociclib with multiple doses of tamoxifen relative to palbociclib administered alone. These results indicate that it is not necessary to adjust palbociclib starting dose when co-administering with tamoxifen. Studies are ongoing evaluating the efficacy of this combination (NCT01864746, NCT02513394).

Cumulative clinical data suggest that a significant number of patients treated with palbociclib experience dose interruptions and delays due to neutropenia without any apparent increase in febrile neutropenia compared to placebo. In addition, preclinical studies suggest that palbociclib exerts an antiproliferative effect on cancer cells that is released when the drug is discontinued Palbociclib Investigator Brochure 2015. These data suggest that a better therapeutic index may be obtained by maintaining continuous exposure using a lower but still biologically relevant dose of palbociclib. Simulated trough and absolute neutrophil profiles based on actual and modelled data indicate that a 100 mg continuous daily dose will be associated with an ANC > 1000 and greater systemic exposure to drug compared with the FDA approved dosing schedule of 125 mg for 3 out of 4 weeks.

This study is designed to provide data regarding the optimal scheduling of palbociclib by comparing the FDA approved schedule of 125 mg daily for 21 out of 28 days to a continuous dosing schedule of 100 mg daily. In addition to evaluating antitumour activity, the safety, tolerability and impact on QOL of the two regimens will be assessed. A specimen biobank will also be compiled using tissue collected on study (see suggestions for future biomarkers studies below).

Quality of Life

Given the incurable nature of advanced breast cancer and the high incidence of treatment related adverse events associated with therapy, patient reported quality of life (QOL) data provide an important perspective on the impact of an intervention, above and beyond treatment induced changes in lifespan. This is especially true for the current proposal which evaluates two different schedules of administration of the same combination of drugs which may have modest differences in disease control but important differences in adverse event and QOL experiences. Further justification of measurement of QOL is provided by previous research demonstrating that QOL data provides additional information to systematically collected adverse event data *[Huschka 2007; Paul 1991]*.

The initial studies evaluating palbociclib did not evaluate QOL in a robust manner. In the trial by Finn et al (2014), QOL was not measured but adverse events were numerically higher in the palbociclib containing arm (including fatigue, arthralgia, alopecia, diarrhea, hot flushes, decreased appetite, dyspnea, vomiting, bone pain, stomatitis, and peripheral neuropathy). Quality of life was collected but not reported in the primary publication of the PALOMA 1 study.

The recently reported phase III trial comparing palbociclib to placebo in combination with fulvestrant in the second line setting measured QOL using the EORTC QLQ C30 and BR23 instruments. Global QOL measurements favoured the palbociclib arm, as did improvement in baseline pain *[Harbeck 2016]*. More data is required to inform the patient perspective on treatment with palbociclib.

In the current study QOL will be collected at predetermined time points during administration of protocol therapy as well as at the time of discontinuation of therapy due to adverse events or progression of disease.

Two instruments will be used to capture the QOL experience of patients, the EORTC QLQ-C30 and a trial specific checklist. The EORTC QLQ-C30 will be used to capture the multidimensionality of QOL in metastatic breast cancer. The EORTC QLQ-C30 is a widely used, cancer specific health-related QOL questionnaire which is well accepted by patients *[Aaronson 1993; Conroy 2004]*. It contains five functional subscales (physical, role, cognitive, emotional, social), three multi-item symptom subscales (fatigue, pain and nausea), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact) and a global health measure (physical condition and global QOL). The questionnaire uses 4 and 7-point scales. For each subscale, the range of possible scores is between 0 and 100. Convergent and criterion validity has been demonstrated for this questionnaire in metastatic breast cancer *[Bottomlay 2004; Mclachlan 1998]* and reliability is adequate *[Aaronson 1993; Hjermstad 1995]*. The EORTC QLQ-C30 has been shown to be responsive to change associated with chemotherapy and with disease progression *[Osoba 1998; Lemieux 2007]*. The questionnaire is available in multiple languages. A trial specific checklist will be added because there are no questions in the EORTC QLQ-C30 regarding mucositis and peripheral neuropathy. The trial specific checklist items were selected following a search of the CCTG QOL data bank and items currently in use in other trials. Completion of the trial specific checklist will be mandatory for all patients. Translations will be provided as necessary. The same scale as used in the EORTC QLQ-C30 will be used.

Correlative Biological Studies

Predictive biomarkers for response to palbociclib are lacking. To date, preclinical and clinical data have identified only estrogen receptor status as a predictive biomarker *[Finn 2014; Jiang 2014]*. Data from the pivotal phase II and III studies in advanced disease show that not all patients with estrogen receptor positive disease will respond to palbociclib and those who respond initially will develop resistant/progressive disease over time *[Finn 2014; Turner 2015]*.

A key correlative study goal will be to survey genomic alterations implicated in G1/S checkpoints. Planned studies on the tumour tissue include CDK2,4,6 mutations status and CNV analysis for CDK2, 4, 6, CCND1-3, CCNE1,2, Rb and p16 using the comprehensive Oncomine panel (Thermofisher). This will form the first clinical comprehensive profiling of the G1/S checkpoint regulators. Exploratory analysis of key genomic alterations may be extended to circulating tumour DNA based on these results.

To address the important unanswered questions regarding identification of biomarkers predictive of response and resistance to palbociclib, a robust and comprehensive biorepository will be assembled as part of this study conduct. Details of the correlative study requirements can be located in section 13.0 of the protocol.

Tumour Collection:
Mandatory archival tissue will be collected from the most recent pathological tumour specimen. This includes metastatic tumour, if available, or from primary tumour resection at first diagnosis of breast cancer.

Tumour specimens will be collected at the time of progression on study for all patients when feasible.

Collection of sequencing samples (cell free DNA, lymphocytes, whole blood and serum/plasma):

Analysis of circulating cell free (tumour) DNA, focusing initially on mutations/alterations in CDK4/6 signaling pathways, will allow researchers to identify key mutations. Over time, these mutations can be used to track the emergence of resistant subclones within patients tumours. With deep sequencing (1500 fold coverage or greater) now possible for known mutations (identified in the pre-treatment biopsies), we will be able to assess the impact of drug treatment on separate clones within the tumour. Circulating markers in serum/plasma have also been shown to provide measures of cell death during treatment phases. Collectively these samples will allow exploration of the mechanisms underlying the emergence of treatment resistance.

Cell-Free DNA and Lymphocyte Collection:
Cell-Free DNA will be collected at baseline and pre-specified time points for exploratory analyses to identify predictive biomarkers of response and resistance to protocol therapy and to examine temporal qualitative and quantitative changes in tumour DNA over time.

Blood lymphocytes will be collected at baseline for studies of pharmacogenomics/ genetic predictors of toxicity and response to protocol therapy.

Collection of Serum and Plasma:
Serum and plasma will be collected at baseline and pre-specified time points for exploratory analyses to identify predictive biomarkers of response and resistance to protocol therapy and to examine temporal qualitative and quantitative changes in proteomic markers over time.

Studies evaluating the impact of the altered dosing schedule on target modulation (RB) in tumour or surrogate tissue are planned pending clarification of methodology. The protocol documents will be modified to incorporate these additions as appropriate.

Summary

In summary, this study will address the hypothesis that the combination of endocrine based anticancer therapy and palbociclib at a dose of 100 mg po daily will result in greater antitumour efficacy due to a greater systemic exposure and fewer dose interruptions of drug compared to the current FDA approved dose and schedule of palbociclib. Importantly, the altered treatment schedule may be associated with a better safety profile including fewer instances of grade 4 neutropenia and febrile neutropenia.

The current proposal will further the scientific and clinical understanding of hormone receptor positive breast cancer treated with palbociclib via the collection of efficacy, quality of life, safety and adverse event data and by the compilation of a comprehensive biorepository of tissues for future correlative biology studies.

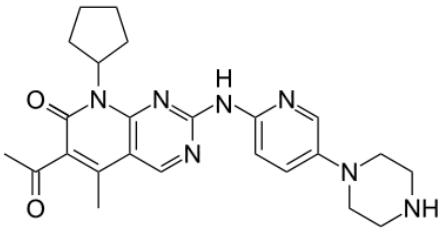
3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Palbociclib

3.1.1 *Name and Chemical Information*

The information provided is in support of PD-0332991-00 (freebase). See the current Palbociclib Investigator Brochure for the most up to date information. PD-0332991-00 capsules will be provided as the active ingredient with precedented excipients filled in hard gelatin capsules composed of gelatin and precedented colorants.

3.1.2 *Chemical Structure*



Molecular Formula: $C_{24}H_{29}N_7O_2$
Molecular Weight: 447.54 daltons

3.1.3 *Mechanism of Action*

Palbociclib, an orally active pyridopyrimidine, is a potent and highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase. Specifically, Palbociclib inhibits CDK4/6-catalyzed phosphorylation of the retinoblastoma protein (Rb), which is required for cell division.

Palbociclib has selectivity for CDK4/6, with little or no activity against a large panel of 274 other protein kinases including other CDKs and a wide variety of tyrosine and serine/threonine kinases.

3.1.4 *Experimental Antitumour Activity*

In human tumour cell lines palbociclib has been shown to have anti-proliferative effects by inhibiting thymidine incorporation into the DNA of a panel of Rb-positive human breast, colon and lung carcinoma cell lines. Additionally, palbociclib has been shown to be effective in preventing cell cycle progression in human leukemias and in nontransformed human epithelial cells and fibroblasts and is equally effective in suppressing cell division in human tumour cell lines (breast and colon). In one model, Colo-205, doses as low as 12.5 mg/kg caused a 13-day growth delay, indicating a 90% inhibition of tumour growth rate. MDA-MB-453 breast carcinoma cells that were exposed to various concentrations of palbociclib for 24 hours show a significant increase in the percentage of cells in the G_1 phase of cell division with a concomitant decline in other phases of the cell cycle. To provide further evidence of the selectivity of palbociclib, the compound was tested against Rb-negative tumour cells, which should not be sensitive to a specific CDK4/6 inhibitor. Palbociclib was tested against the MDA-MB-468 human breast carcinoma and the DU-145 prostate tumour models, both of which are Rb-negative. Palbociclib had no anti-proliferative activity on these cells. Thus, evidence indicates that palbociclib induces anti-tumour activity due to the inhibition of CDK4/CDK6 protein kinase activity.

Further studies investigated whether continuous daily dosing of palbociclib was needed for optimal efficacy. Four dosing schedules were employed against the MDA-MB-435 breast carcinoma model over 14 days of treatment, including continuous daily, every other day, every third day, and 3 courses of 3 days dosing followed by 4-day drug holidays. The design of this experiment was such that the total compound administered over the 2-week period was identical for each treatment schedule. The results show that a similar degree of efficacy was attained with all schedules, implying that an intermittent regimen is feasible without compromising activity. Similar experiments were conducted against the Colo-205 colon carcinoma model. Again, intermittent schedules were as efficacious as daily dosing, with tumour regressions occurring during all dosing regimens.

In parallel with the in vivo efficacy tests, tumours were harvested for pharmacodynamics analysis to ensure that anti-tumour activity correlated with modulation of the target and to provide confidence that the proposed biomarker would predict for efficacy. Efficacious and non-efficacious doses of palbociclib were given to mice bearing the MDA-MB-435 breast carcinoma and the phosphorylation status of serine-780 on Rb in tumour tissue was monitored over time. The results show that while all doses caused a reduction in the biomarker shortly after drug administration, phosphorylation returned at the non-efficacious doses (12.5 and 37.5 mg/kg) over the 24-hour interval before the next dose. However, the highly efficacious dose of 150 mg/kg suppressed Rb serine-780 phosphorylation during the full 24-hour period. These data suggest that complete suppression of Rb phosphorylation needs to be maintained between drug doses to achieve significant efficacy against this particular tumour model. Because the lower doses result in transient target modulation, more frequent dosing at these doses might result in improved efficacy by maintaining suppression of phosphorylation. Similar experiments with the Colo-205 colon carcinoma xenografts, which are exquisitely sensitive to palbociclib, shows that complete suppression of Rb phosphorylation between doses was found to be unnecessary for producing growth inhibition. However, for maximal effects against Colo-205 tumours (i.e. regression), total inhibition had to be maintained.

3.1.5 *Animal Toxicology*

Palbociclib was administered to rats and dogs in toxicity studies up to 39 weeks in duration, with a dosing regimen of 3 weeks of dosing followed by a 1-week non-dosing period. The no observed adverse effect levels (NOAELs) in the 27-week and 39-week toxicity studies were at <10 (males) and <50 (females) mg/kg/day in the rat and <0.2 (males) and 3.0 (females) mg/kg/day in the dog. Systemic exposure (AUC24) associated with the 10 and 50 mg/kg/day doses in male and female rats were 6000 and 2650 ng•h/mL, respectively, and with the 0.2 and 3.0 mg/kg/day doses in male and female dogs were 96.6 ng•h/mL and 2050 ng•h/mL, respectively. The primary toxicities identified from these studies included hematolymphopoietic effects; altered glucose metabolism and related effects on the pancreas, eye, teeth, kidney, and adipose tissue; and effects on bone, male reproductive organs, and embryofetal development. Other palbociclib-related findings were in gastrointestinal tissue, appeared as vacuolation in multiple tissues, and included effects on the liver, kidney, adrenal gland, and respiratory system, and prolonged coagulation time that were of limited severity and/or lacked degenerative features. Dose-related decreases in body weight and/or food consumption were observed following single and repeat dosing, and moribundity preceded by clinical signs of intolerance was observed at ≥100 mg/kg/day in rats and ≥ 10 mg/kg/day in dogs at doses where systemic unbound AUC24 exposures (≥ 3663 ng•h/mL and ≥ 10119 ng•h/mL, respectively) exceeded those considered clinically relevant. In genetic toxicity tests, palbociclib was identified as an aneugen, with a NOAEL for micronuclei formation at 50 mg/kg/day (unbound C_{max} 225 ng/mL and AUC24 of 2163 ng•h/mL).

3.1.6 *Clinical Trials*

A total of 400 healthy volunteers have received single doses of palbociclib, ranging from 50 mg to 150 mg as of the December 10, 2014 data cut off of the February 2015 Investigator Brochure. The most frequently reported treatment-emergent adverse events (TEAEs) of any grade, regardless of causality were nausea, headache, diarrhea, abdominal distention, dizziness, somnolence, abdominal discomfort, fatigue and back pain. The most frequently reported TEAEs of any grade, considered related to study treatment were headache, nausea, somnolence and abdominal distention. In the healthy volunteer studies abnormal laboratory values were not necessarily considered adverse events, however, neutropenia and lymphocytopenia were frequently observed (14.5% and 11.5% of patients, respectively).

Palbociclib has been administered to over 281 subjects with cancer in both monotherapy and combination therapy regimens in phase I-III clinical trials at doses up to 225 mg. The most frequently reported TEAEs (≥ 20% of patients) of any grade (regardless of causality) for palbociclib administered as a single agent are neutropenia, thrombocytopenia, anemia, fatigue, constipation, nausea, decreased appetite, vomiting and diarrhea. In all clinical studies, neutropenia has been among the most frequently associated adverse event.

Please refer to the most recent version of the Investigator Brochure for the detailed risk profile.

3.1.7 Pharmacokinetic Studies

As of December 10, 2014, twenty-one clinical studies have evaluated the PK of palbociclib. Four of these trials were conducted in patients with advanced malignant disease. Seventeen phase I clinical pharmacology and biopharmaceutic studies of palbociclib were conducted in healthy subjects. Ten of these 17 clinical trials were clinical pharmacology studies conducted to investigate the absorption, distribution, metabolism, and excretion of palbociclib as well as examine the potential for DDI with palbociclib. The remaining 7 of the 17 clinical trials were biopharmaceutic studies conducted to examine the bioavailability, bioequivalence, and food effect of the palbociclib formulations.

Pharmacokinetic (PK) data from patients with advanced cancer from Study A5481001 indicate that the plasma pharmacokinetics of palbociclib are low to moderately variable with generally dose proportional exposures over the dose range evaluated (25 mg to 225 mg) following single and multiple doses. PK data from Studies A5481001, A5481003, and A5481010 indicate that palbociclib is slowly absorbed with a median time of maximum concentration (T_{max}) between 4 and 8 hours post-dose, and is slowly eliminated with an elimination half-life ($t_{1/2}$) ranging from 23.2 hours to 28.8 hours. Palbociclib accumulates after repeated daily dosing (median Rac ranged from 1.9 to 2.4), which was consistent with its terminal $t_{1/2}$. In Study A5481010, the median R_{ss} (the predicted accumulation to estimate linearity) was 1.1, indicating that palbociclib clearance does not change over time. In Study A5481003, palbociclib was shown to achieve steady-state concentrations following 8 days of QD dosing. The palbociclib geometric mean volume of distribution (V_z/F) was 2583 L in women with advanced breast cancer (Study A5481003), which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues.

In humans, metabolism is the major route of elimination of palbociclib. Following a single oral administration of [^{14}C]palbociclib to healthy subjects (Study A5481011), the overall median recovery of the administered radioactivity in the excreta was 91.6% with a median of 17.5% recovered in urine and a median of 74.1% recovered in feces. Excretion of unchanged palbociclib in the feces and urine was 2.3% and 6.9% of dose, respectively, indicating that excretion plays a minor role in elimination of palbociclib. A study in healthy volunteers (A5481015) indicated that the absolute oral bioavailability of palbociclib was approximately 46%.

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. Data from studies involving co administration of palbociclib with strong CYP3A inducers and inhibitors demonstrate important changes in the PK of palbociclib and thus concurrent administration of these types of drugs with palbociclib should be avoided (studies A5481016, A5481017).

Food exposure affects the PK of palbociclib by increasing the AUC inf and C Max by 12-38% depending on fat content when food is given 1 hour before and or 2 hours after palbociclib administration (A5481021). In addition, food intake significantly reduces the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib commercial free base capsules should be taken with food.

The co-administration of drugs that alter the gastric pH such as proton pump inhibitors, local antacids or H2 receptor antagonists does not meaningfully impact palbociclib exposure when palbociclib is taken with food (study A5481038).

Data from a DDI study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when IBRANCE was given alone.

Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST), has no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl < 60 mL/min). Palbociclib exposure in not affected by mild or moderate renal impairment (30 mL/min ≤ CrCl). The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment.

A pharmacokinetic/pharmacodynamic analysis to evaluate the relationship between palbociclib exposure and ECG endpoints (RR and QTc intervals) were developed using pooled data from 3 clinical trials in patients with advanced malignant disease (Studies A5481001, A5481002, and A5481003). The study population consisted of 48 men and 136 women with a median (range) body weight of 73.0 (37.9-123) kg and age of 61.5 (22-89) years old. Palbociclib doses ranged from 25 mg to 225 mg QD. The data collected from 184 patients consisted of 569 ECG-palbociclib concentration-matched pairs; the observed plasma concentrations had a median (range) of 55.2 (2.51-329) ng/mL. The average heart rate, RR, QT, QT corrected for heart rate according to Bazett (QTcB), QT corrected for heart rate according to Fridericia (QTcF), and QTcS (QT interval corrected for heart rate according to a study-specific correction factor) at baseline for ECG-palbociclib concentration matched data were 76.8 beats per minute, 808 msec, 380 msec, 425 msec, 409 msec, and 412 msec, respectively.

The results of the analysis indicate that palbociclib does not appear to have a concentration-dependent effect on heart rate. A slight positive linear relationship between palbociclib concentration and QTcS was observed; however, at the mean or median steady-state palbociclib C_{max} following administration of the recommended clinical dose of palbociclib (125 mg QD) in patients with cancer, the upper bound of the one-sided 95% CI for the increase in QTcS fell below the threshold of 10 msec, suggesting that QT prolongation is not a safety concern for palbociclib at the recommended clinical dose according to the criteria described in the ICH guidance for Industry E14. Similar results were obtained when QTcF and QTcB were used.

3.1.8 *Pharmaceutical Data*

Supplied:
Palbociclib is an oral capsule and will be supplied in three strengths: 75 mg, 100 mg, or 125 mg.

Stability:
The shelf life of Palbociclib will be indicated on the label

Storage:
Palbociclib must be stored at room temperature (15ºC to 30ºC)

Route of Administration:
Orally

3.2 Endocrine Therapy

The following standard of care endocrine treatment agents are allowed for each treatment arm:

- Tamoxifen
- Non-steroidal aromatase-inhibitors (anastrozole, letrozole)
- Steroidal aromatase inhibitor (exemestane)
- Fulvestrant

Ovarian suppressive therapy (LHRH agonists, surgical or radiologic ablation of the ovaries) is required for pre-menopausal women who will be treated on study with fulvestrant or an aromatase inhibitor and is optional for premenopausal women who will be treated on study with tamoxifen.

All standard of care agents will be administered at the discretion of the principal investigator (or his/her designee) as well as according to standard institutional or regional practice.

Administration of endocrine therapy is performed on an outpatient, self-administration basis according to local requirements and local standard practice. On days when patient is scheduled for a clinic visit, the patient should take scheduled endocrine therapy dose once all visit assessments have been performed (either at home or in the clinic) unless otherwise indicated.

4.0 TRIAL DESIGN

This is an open label multi-centre, multi-national randomized phase II trial of two different dose regimens of palbociclib in combination with fulvestrant or tamoxifen or AI in women with ER positive, HER2 negative advanced/metastatic breast cancer.

4.1 Stratification

Patients will be stratified by:

- Centre
- Visceral metastases: yes vs. no
- Duration of exposure to most recent endocrine therapy prior to randomization: ≥ 6 months versus < 6 months in the advanced/metastatic setting or ≥ 24 months versus < 24 months in adjuvant setting
- Planned use of Fulvestrant versus Tamoxifen versus Aromatase Inhibitor

4.2 Randomization

Patients will be randomized (1:1) to receive one of the following treatments, to a planned sample size of 180 patients.

<table>
<tr><td colspan="6">Patients will be randomized to one of the following two arms:</td></tr>
<tr><td>Arm</td><td>Agent(s)</td><td>Dose</td><td>Route</td><td>Schedule</td><td>Duration</td></tr>
<tr><td rowspan="7">1</td><td rowspan="7">Endocrine Therapy</td><td>Palbociclib 100 mg</td><td>PO</td><td>Daily for 28 day cycle</td><td rowspan="7">Treat until progressive disease</td></tr>
<tr><td>Fulvestrant* 500 mg</td><td>IM</td><td>Days 1 and 15 of cycle 1 and then on day 1 of each 28 day cycle</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td>Tamoxifen** 20 mg</td><td>PO</td><td>Daily for 28 day cycle</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td>Aromatase Inhibitor*:
Letrozole 2.5 mg
Anastrozole 1 mg
Exemestane 25 mg</td><td>PO</td><td>Daily for 28 day cycle</td></tr>
<tr><td rowspan="7">2</td><td rowspan="7">Endocrine Therapy</td><td>Palbociclib 125 mg</td><td>PO</td><td>Days 1-21 of each 28 day cycle</td><td rowspan="7">Treat until progressive disease</td></tr>
<tr><td>Fulvestrant* 500 mg</td><td>IM</td><td>Days 1 and 15 of cycle 1 and then on day 1 of each 28 day cycle</td></tr>
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Letrozole 2.5 mg
Anastrozole 1 mg
Exemestane 25 mg</td><td>PO</td><td>Daily for 28 day cycle</td></tr>
<tr><td colspan="6">* In premenopausal women ovarian suppression therapy is required
** In premenopausal women ovarian suppression therapy is optional</td></tr>
</table>

5.0 STUDY POPULATION

Women with documented evidence of estrogen receptor positive HER2 negative breast cancer, which is recurrent or advanced/metastatic, who have received one previous line of prior endocrine therapy in the adjuvant or metastatic setting.

5.1 Eligibility Criteria

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

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 fulfil all of the following criteria to be eligible for admission to the study:

5.1.1 Premenopausal and postmenopausal women 18 years of age or older.

5.1.2 Histologically confirmed adenocarcinoma of the breast, with ER positive and HER2 negative status based on local testing on most recent pathological tumour specimen.

5.1.3 Patients must satisfy the following criteria for prior therapy:

- Progressed during treatment or within 12 months of completion of adjuvant endocrine therapy

OR

- Progressed during prior endocrine therapy for advanced/metastatic disease.

Note: 'Progressed during endocrine therapy' means that the patient progressed while on or within 1 month after discontinuation of endocrine therapy.

5.1.4 One line of chemotherapy for advanced/metastatic disease (regardless of prior adjuvant chemotherapy use) is allowed in addition to endocrine therapy.

5.1.5 Patients must have evidence of disease to be eligible for the study, but measurable disease is not mandatory.

5.1.6 For those patient with measureable disease who will be included in the response assessment, the following criteria must apply:

- X-ray ≥ 20 mm
- Spiral CT scan or physical exam ≥ 10 mm (lymph nodes must be ≥ 15 mm in the short axis)
- Conventional CT scan, MRI ≥ 20 mm
- Measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented.

Tumour lesions previously irradiated or subjected to other loco regional therapy will only be deemed measurable if progression at the treated site after completion of therapy is clearly documented.

5.1.7 Eastern Cooperative Oncology Group (ECOG) 0-2.

5.1.8 Adequate organ and bone marrow function as defined by:

- ANC ≥ 1,500/mm3 (1.5 x 109/L);
- Platelets ≥ 100,000/mm3 (100 x 109/L);
- Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution;
- Total serum bilirubin ≤ 1.5 x ULN (<3 ULN if Gilbert's disease).

5.1.9 Patient must agree to provide tumour tissue from the most recent pathological tumour specimen. Local policy must permit the submission of tissue (blocks or cores). It is the centres responsibility to notify CCTG immediately of any changes in local policy that would preclude the submission of tissue. Failure to provide tissue blocks or cores will render the patient ineligible. Please refer to Section 13.0 for additional information.

5.1.10 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French. The baseline assessment must be completed within the required timelines, prior to registration/randomization. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

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

A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.

5.1.12 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 placed on patients being considered for this trial (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, response assessments and follow-up.

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

5.1.14 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, bilateral tubal ligation, ovarian ablation by radiation therapy 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, she is responsible for beginning contraceptive measures.

Women of childbearing potential receiving combination therapy palbociclib plus tamoxifen or any endocrine therapy plus LHRH analogue must use effective contraception as described above.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Appendix I); 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.

5.2 Ineligibility Criteria

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

5.2.1 Patients with advanced, symptomatic, visceral spread that are at risk of life threatening complication in the short term.

5.2.2 Patients with symptomatic CNS involvement, meningeal or parenchymal, that is uncontrolled or requires steroids.

5.2.3 Prior treatment with any CDK 4/6 inhibitor.

5.2.4 Prior treatment with mTOR inhibitors.

5.2.5 Active second malignancy, regardless of ongoing treatment.

5.2.6 Any concurrent medical condition that in the opinion of the investigator would interfere with the safe administration of the study drug and participation in the study.

5.2.7 Participation in a prior anti-cancer investigational study within 30 days prior to enrollment.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• History including: – Diagnosis – Prior Therapy – Concurrent Illnesses – Concomitant Medication • Physical Exam including: – Height and Weight – Blood Pressure and Pulse – ECOG Performance Status	Within 14 days prior to randomization
Hematology	• CBC • Differential • Hemoglobin A1c (HBA1c)	Within 14 days prior to randomization
Biochemistry	• Serum creatinine • Bilirubin (total)	Within 14 days prior to randomization
Radiology	• CT/MRI of chest, abdomen and pelvis • Bone Scan or PET* • Other imagining as necessary to document all sites of disease	Within 28 days prior to randomization
Other Investigations	• Pregnancy test (if applicable)** • ECG • Urinalysis	Within 14 days prior to randomization
Adverse Event	• Baseline adverse event evaluation (to document residual adverse events from previous therapy and baseline symptoms)	Within 14 days prior to randomization
Correlative Studies	• Submission of representative block or core of available tumour tissue from the primary breast cancer or metastatic lesion to central tumour bank	On request
	• Whole blood for cfDNA and lymphocyte extraction*** • Whole blood, serum and plasma for banking***	Pre Day 1-Cycle 1 dose
Quality of Life	• EORTC QLQ-C30 • Trial Specific Checklist (see Appendix VI)	Within 14 days prior to randomization

* Per Institutional Standard (mandatory for patients with bone only disease).

** Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.

*** Mandatory whole blood collection for cell-free DNA and lymphocytes for all patients; Optional whole blood, serum and plasma banking for consenting patients.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations 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/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the MA.38 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the MA.38 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 MA.38)
- investigator CCTG user ID
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- stratification factors

7.2 Stratification

Subjects will be stratified by:

- Centre
- Visceral Metastases: yes versus no
- Duration of exposure to most recent endocrine therapy prior to randomization: $\geq$ 6 months versus < 6 months in the advanced/metastatic setting, or $\geq$ 24 months versus < 24 months in the adjuvant setting
- Planned use of Fulvestrant versus Tamoxifen versus Aromatase Inhibitor

7.3 Randomization

Randomization 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, may 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 eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus a minimal follow-up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

8.0 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 randomization.

8.1 Treatment Plan

8.1.1 *Drug Administration*

<table>
<tr><td colspan="6">Patients will be randomized to one of the following two arms:</td></tr>
<tr><td>Arm</td><td>Agent(s)</td><td>Dose</td><td>Route</td><td>Schedule</td><td>Duration</td></tr>
<tr><td rowspan="7">1</td><td>Palbociclib</td><td>100 mg</td><td>PO</td><td>Daily for 28 day cycle</td><td rowspan="7">Treat until progressive disease</td></tr>
<tr><td rowspan="6">Endocrine Therapy</td><td>Fulvestrant* 500 mg</td><td>IM</td><td>Days 1 and 15 of cycle 1 and then on day 1 of each 28 day cycle</td></tr>
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<tr><td>Tamoxifen** 20 mg</td><td>PO</td><td>Daily for 28 day cycle</td></tr>
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Anastrozole 1 mg
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<tr><td rowspan="7">2</td><td>Palbociclib</td><td>125 mg</td><td>PO</td><td>Days 1-21 of each 28 day cycle</td><td rowspan="7">Treat until progressive disease</td></tr>
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<tr><td colspan="6">* In premenopausal women ovarian suppression therapy is required
** In premenopausal women ovarian suppression therapy is optional</td></tr>
</table>

8.2 Palbociclib

Patients should be instructed to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day.

Palbociclib capsules should be taken with food.

Patients experiencing investigational product related toxicity may have their dose modified according to Section 8.2.3.

General rules for palbociclib administration:

- Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.
- Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose.

8.2.1 *Premedication*

Premedication is not expected to be required.

8.2.2 *Patient Monitoring*

All patients should be closely monitored according to guidelines in Section 9.0 and be advised to contact the treating centre in the case of significant toxicities.

8.2.3 *Dose Adjustments*

Doses will be 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 Version 4 (CTCAE) (see Appendix V).

The major toxic effects of Palbociclib which limit dose are neutropenia, thrombocytopenia, anemia, fatigue, constipation, nausea, decreased appetite, vomiting and diarrhea. 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.

In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery followed by dose reduction (if required).
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.
- At start of the new cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients discontinuing palbociclib treatment due to treatment-related toxicity may continue endocrine therapy, as per the investigator's discretion.

The Palbociclib dose will be decreased according to the schedule displayed in the following table:

	Starting Dose	1st Reduction	2nd Reduction	3rd Reduction
Arm 1	100 mg	75 mg	discontinue	NA
Arm 2	125 mg	100 mg	75 mg	discontinue

A dose of 75 mg represents the lowest does that a patient can receive. Dose escalation after a dose reduction is not permitted.

8.2.3.1 *Palbociclib Dose Management for Hematologic Adverse Events*

Applies to Arm 1 (continuous daily dosing) during a cycle. See 8.2.4 for day 1 modifications:

CTCAE Grade	Palbociclib Dose Management
Grade 1 ANC < LLN to 1500/mm^3 Platelets < LLN to 75K/mm^3	• No dose adjustment is required.
Grade 2 ANC < 1500 - 1000/mm^3 Platelets < 75K - 50K/mm^3	• No dose adjustment is required.
Grade 3 ANC < 1000-500/mm^3 Platelets < 50K - 25K/mm^3	• Reduce by one dose level immediately, and continue treatment. • Repeat complete blood count monitoring one week later, continue treatment if Grade < 3 for duration of cycle. • If grade 3 persists, withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2.[A,B] • Repeat complete blood count monitoring on day 14 of next cycle. • If event recurs next cycle, withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2, and then continue with daily dosing schedule of 3 out of 4 weeks. [A,B]
Grade 3 neutropenia with fever +/- infection ANC < 1000 mm^3 and fever ≥ 38.5º C +/- infection	• Withhold Palbociclib and initiation of next cycle until recovery to Grade ≤ 2 (≥ 1000/mm^3).[A,B] • Resume at next lower dose. [C]
Grade 4 ANC < 500/mm^3 Platelets < 25 K	• Withhold Palbociclib and initiation of next cycle until recovery to Grade ≤ 2.[A,B] • Resume at next lower dose. [C]
[A] Patients treated on study with fulvestrant may delay initiation of next cycle until Palbociclib is resumed. [B] If no recovery within 28 days of dose interruption, discontinue Palbociclib. [C] If event recurs at 75 mg daily dose, discontinue Palbociclib.	

Applies to daily dosing 3 out of 4 weeks during a cycle. See 8.2.4 for day 1 modifications:

CTCAE Grade	Palbociclib Dose Management
Grade 1 ANC < LLN to 1500/mm^3 Platelets < LLN to 75K/mm^3	• No dose adjustment is required.
Grade 2 ANC < 1500 - 1000/mm^3 Platelets < 75K - 50K/mm^3	• No dose adjustment is required.
Grade 3 ANC < 1000-500/mm^3 Platelets < 50K - 25K/mm^3	• No dose adjustment is required. • Consider repeating complete blood count monitoring one week later. • Withhold initiation of next cycle until recovery to Grade ≤ 2.[A,B]
Grade 3 neutropenia with fever +/- infection ANC < 1000 mm^3 and fever ≥ 38.5º C +/- infection	• Withhold Palbociclib and initiation of next cycle until recovery to Grade ≤ 2 (≥ 1000/mm^3).[A,B] • Resume at next lower dose. [C]
Grade 4 ANC < 500/mm^3 Platelets < 25 K	• Withhold Palbociclib and initiation of next cycle until recovery to Grade ≤ 2.[A,B] • Resume at next lower dose. [C]
[A] Patients treated on study with fulvestrant may delay initiation of next cycle until Palbociclib is resumed. [B] If no recovery after 28 days of dose interruption, discontinue Palbociclib. [C] If event recurs at 75 mg daily dose, discontinue Palbociclib.	

8.2.3.2 *Palbociclib Dose Management for Liver and Renal Impairment*

Bilirubin Total	Palbociclib Dose Management
Grade 1 (≥ ULN - 1.5 x ULN)	• No dose adjustment is required
Grade 2 (> 1.5 - 3.0 x ULN)	• No dose adjustment required (if not considered a safety risk for the patient)
≥ Grade 3 (> 3.0 X ULN)	• Hold Palbociclib until recovered to ≤ grade 1 or ≤ grade 2 (if not considered a safety risk for the patient).[A,B] • Resume treatment at 1 dose level lower.
[A] Patients treated on study with fulvestrant may delay initiation of next cycle until Palbociclib is resumed. [B] If no recovery within 28 days of dose interruption, discontinue Palbociclib.	

Creatinine Clearance	Palbociclib Dose Management
Grade 1 (<LLN - 60 ml/min) or Grade 2 (59-30 ml/min)	• No dose adjustment is required
≥ Grade 3 (< 30 ml/min)	• Hold Palbociclib until recovered to ≤ grade 1 or ≤ grade 2 (if not considered a safety risk for the patient). [A,B] • Resume treatment at 1 dose level lower
[A] Patients treated on study with fulvestrant may delay initiation of next cycle until Palbociclib is resumed. [B] If no recovery within 28 days of dose interruption, discontinue Palbociclib.	

8.2.3.3 *Palbociclib Dose Management for Other Non-hematologic Adverse Events*

In case of clinically significant toxicities, please follow the instructions in the table below.

CTCAE Grade	Palbociclib Dose Management
Grade 1 or Grade 2	• No dose adjustment is required.[A]
≥ Grade 3 (if persisting despite medical treatment)	• Hold Palbociclib until recovered to ≤ grade 1 or ≤ grade 2 (if not considered a safety risk for the patient).[B,C] • Resume treatment at 1 dose level lower

[A] In case of a Grade 2 toxicity (excluding alopecia) lasting for ≥ 28 days (both assessed in the presence of maximum supportive care as judged by the investigator), dose reduction is recommended for the subsequent cycles.

[B] Patients treated on study with fulvestrant may delay initiation of next cycle until Palbociclib is resumed.

[C] If no recovery within 28 days of dose interruption, discontinue Palbociclib.

Treatment-related GI tract events have been commonly observed when palbociclib is used as monotherapy or in combination with other anticancer therapies. The most frequent treatment-related events in this system organ class were nausea, diarrhea, and vomiting. Most occurrences were mild (Grade 1). Since GI events can contribute to the occurrence of dehydration, decreased food intake, weight loss and fatigue, patients should be closely monitored for such events. Supportive treatment measures may be initiated as deemed necessary by the treating physician in agreement with best local clinical practices.

8.2.4 *Retreatment Criteria (and day 1 of a cycle)*

Retreatment with palbociclib following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥ 50,000/mm^3.
- ANC ≥ 1000/mm^3 and no fever.
- Total Bilirubin ≤ 1.5 x ULN.
- Creatinine Clearance ≥ 30 ml/min.
- Grade ≥ 3 non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment) have recovered to Grade ≤ 1 or ≤ grade 2 (if not considered a safety risk for the patient) or baseline.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be adjusted as clinically indicated. If the retreatment parameters are met within 28 days of treatment interruption or cycle delay, palbociclib may be resumed. Refer to the Dose Adjustment section above for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 28 days of dose interruption or cycle delay (including the planned 1 week off treatment at the end of the cycle), the patient should permanently discontinue palbociclib treatment. Any request for exception to this rule must be discussed with the sponsor.

8.2.5 *Duration of Therapy*

Unless unmanageable adverse events occur, treatment with palbociclib will be given until disease progression.

8.2.6 *Patient Compliance*

Compliance with Palbociclib is very important to the objectives of this study. Study site pharmacy staff will make capsule counts at each patient visit during treatment. Patients will be instructed to notify study site personnel of missed doses. Dates of missed, held or reduced doses will be recorded on the case report form.

8.3 Endocrine Therapy

Patients will receive either fulvestrant or tamoxifen or aromatase inhibitor hormonal therapy based on investigator/patient preference. The selected therapy must be different than the most recent line of endocrine therapy. Premenopausal women are required to undergo ovarian suppression therapy in addition to fulvestrant or aromatase inhibitor therapy (i.e. surgery, radiation or biochemical ablation by LHRH therapy).

Endocrine therapy may be administered as per local policies/procedures.

8.4 Concomitant Therapy

8.4.1 *Permitted*

Patients should receive full supportive care (including bisphosphonates) and palliative care (e.g. pain control) as clinically indicated during the trial, including transfusion of blood products, and treatment with antibiotics, antiemetics, antidiarrheals and analgesics when appropriate - except for those medications identified as “excluded” as listed in Section 8.4.2.

Bisphosphonates for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to study entry. However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the patient’s source documentation.

Patients may receive localized radiotherapy on study provided that this therapy is not being given because of progression of disease, and provided it is not given to a target lesion. Patients who receive radiation therapy to treat a progressing disease lesion, even if the intent is palliative, should come off protocol therapy.

8.4.2 *Not Permitted*

Concurrent administration with other non-protocol anti-cancer therapy (including hormonal therapy), radiation therapy or investigational treatment is not permitted.

Cytochrome P450 inhibitors or Inducers:
Palbociclib is primarily metabolized by liver enzymes, particularly CYP3A4. Co-administration of potent inhibitors or inducers of this enzyme can result in significant changes in exposure to Palbociclib. For this reason, concomitant administration of agents known to strongly inhibit or strongly induce CYP3A4 isoenzymes is not permitted before or during the study. Moderate or weak inducers or inhibitors should be used with caution.

A comprehensive list of CYP3A4 inhibitors and inducers is provided in Appendix VIII. The Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. If any of the not permitted concomitant medications listed in Appendix VIII become necessary for patient management, please contact the CCTG to discuss appropriate washout periods and possible drug interactions.

The dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with palbociclib.

Glucocorticosteroids (oral):
Oral glucocorticosteroid use is not allowed during Palbociclib treatment unless absolutely necessary (e.g. for treatment of adverse events) or short-term (up to 2 weeks) because many such steroids effectively lower Palbociclib exposure through CYP3A4 interactions. See Appendix VIII for a list of prohibited oral glucocorticosteroid medications.

The concomitant use of proton-pump inhibitors (PPI) with palbociclib is allowed. Investigators should use caution for patients receiving concurrent treatment with these acid reducing agents, as well as H2-receptor antagonists (H2RAs).

CYP2D6 inhibitors: for patients receiving tamoxifen, the concomitant use of CYP2D6 inhibitors (including, but not limited to, paroxetine, fluoxetine, sertraline, quinidine) is not recommended.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

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

9.1 Evaluation During Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• History • Weight • ECOG performance status • Blood pressure and pulse • Concomitant medications	• Day 1 of each cycle
Hematology*	• CBC • Differential	• Every 2 weeks for the first 2 cycles and then on day 1 of each cycle thereafter
	• Hemoglobin A1c (HBA1c)**	• Day 1 of every 3rd cycle (i.e. cycle 3, 6, 9, 12, etc.)
Biochemistry*	• Serum creatinine • Bilirubin	• Day 1 of each cycle
Radiology	• CT/MRI of chest, abdomen and pelvis	• Every 12 weeks from randomization (CT schedule must be maintained)
	• Bone Scan or PET	• Every 12 weeks from randomization for patients with bone only disease (schedule must be maintained) • As clinically indicated for all other patients
	• Other imagining as necessary to document all sites of disease	• As clinically indicated
Other Investigations	• Pregnancy test • ECG • Urinalysis • Ophthalmology exam	• As clinically indicated
Adverse Events***	• Patients must be evaluated after each cycle for adverse events	
Correlative Studies	• Whole blood for cfDNA extraction**** • Plasma and serum for banking****	• Every 12 weeks from randomization and at the time of relapse/ progression
	• Tissue biopsy at time of progression	• At time of progression (if feasible)
Quality of Life	• EORTC QLQ-C30 • Trial Specific Checklists	• At 4, 8 and 12 weeks and then every 12 weeks until progressive disease

* Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.

** If HBA1c results are substantially abnormal, an ophthalmology exam is indicated.

*** Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) (Appendix V).

**** Mandatory whole blood collection for cell-free DNA for all patients; Optional serum and plasma banking for consenting patients.

9.2 Evaluation After Protocol Treatment

After discontinuation of study treatment, survival status (including start, stop and type of post study anticancer therapies) will be collected at 4 weeks post treatment, then every 3 months (i.e., month 3, 6, and 9, +/- 14 days) then every 6 months starting at Month 12 (+/- 14 days) from the last dose of study treatment.

For patients who discontinue study treatment for reasons other than radiographically and/or clinically (i.e. for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumour assessment performed during the follow-up visits every 12 weeks (+/-7 days calculated from the date of randomization) until disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (e.g. death, patient's request, lost to follow-up), whichever occurs first.

For patients who discontinue study treatment due to objective disease progression, telephone contact is acceptable (with the exception of the 4 week follow-up visit).

Investigations		Timing
History and Physical Exam including:	• History	• at each visit
	• Weight • ECOG performance status • Blood pressure and pulse	• at each visit until disease progression
	• Concomitant medications	• at the 4 week visit only
Hematology	• CBC • differential • Hemoglobin A1c (HBA1c)*	• at the 4 week visit only
Biochemistry	• Serum creatinine • Bilirubin	• at the 4 week visit only
Radiology	• CT/MRI of chest, abdomen and pelvis	• every 12 weeks from randomization until disease progression (ct schedule must be maintained) then as clinically indicated
	• Bone scan or PET	• every 12 weeks from randomization for patients with bone only disease (schedule must be maintained) • as clinically indicated for all other patients
	• Other imagining as necessary to document all sites of disease	• as clinically indicated
Other Investigations	• Pregnancy test • ECG • Urinalysis • Ophthalmology exam	• as clinically indicated
Adverse Events	• Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) (Appendix V).	• at each visit**

continued on next page …

Investigations		Timing
Correlative Studies	• Whole blood for cfDNA extraction*** • Serum and plasma for banking***	• every 12 weeks from randomization and at the time of relapse/ progression
	• Tissue biopsy at time of progression	• at time of progression (if feasible)
Quality of Life	• EORTC QLQ-C30 • Trial Specific Checklists	• at 4, 8 and 12 weeks and then every 12 weeks until progressive disease

* If HBA1c results are substantially abnormal, an ophthalmology exam is indicated.

** Only Adverse Events deemed related to protocol therapy (Palbociclib, Fulvestrant or Tamoxifen or AI).

*** Mandatory whole blood collection for cell-free DNA for all patients; Optional serum and plasma banking for consenting patients

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

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

10.1.2 Evaluable for response. All patients who have received at least one dose 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]*.

10.1.3 Evaluable for quality of life assessment. All patients who have completed at least one quality of life questionnaire are evaluable for quality of life.

10.2 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.

10.2.1 *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 ≥ 15mm 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.

10.2.2 *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.

10.2.3 *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 10.2.4). 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 can not 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.

10.2.4 *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".

10.2.5 *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 < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [ref RECIST 1.1]) before CR can be accepted. Confirmation of response is not required.

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 not required.

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 <10mm
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 < 10mm
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.

10.3 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).

10.4 Stable Disease Duration

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

10.5 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".

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

10.5.2 *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.

10.5.3 *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 [ref RECIST 1.1]. 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).

10.5.4 *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.

10.5.5 *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.

10.5.6 *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.

11.0 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 V). 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.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

All deaths, regardless of causality or relation to protocol treatment, must be reported in an expedited manner. This includes deaths occurring during the treatment period, and within 30 days after the date of the final dose (or at any time if the investigator suspects the death to be treatment related).

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.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the MA.38 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

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

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

FAX paper SAE Report to:

MA.38 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

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

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

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the MA.38 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).

11.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

11.3.1 *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 5.1.14.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants. Pregnancies occurring up to 90 days 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.

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 partner of trial participant (and 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.

11.3.3 *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.

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. 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.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

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

11.5 CCTG Reporting Responsibility to Pfizer

Pfizer Inc. will be notified of all protocol reportable serious adverse events (Section 11.1) and provided with the corresponding completed CCTG MA.38 CIOMS report within one working day (immediately if the event is fatal or life-threatening) of first awareness of the event. Additionally, Pfizer Inc. will be notified of all incidences of exposure to Palbociclib during pregnancy or lactation.

Pfizer Inc. will also be notified of all deaths on protocol therapy, and within 30 days of the last dose of protocol therapy, regardless of causality or relation to protocol treatment within one working day of first awareness of the event.

11.6 Pfizer Reporting Responsibilities

Pfizer will provide CCTG with a copy of the current Investigator's Brochure and Safety Letters / Safety Updates from other studies with Palbociclib reported to regulatory authorities in a timely manner.

11.7 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 MA.38 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 MA.38 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.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 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 8.0.
- Tumour progression as defined in Section 10.0.
- Request by the patient. 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.

12.2 Duration of Protocol Treatment

In the event of progressive disease, patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and are, in the opinion of the investigator, continuing to derive clinical benefit from protocol treatment.

Patients will be permitted to remain on protocol therapy beyond formal objective progression until the Investigator believes the patient is no longer deriving benefit. Continued use of fulvestrant is permitted, but this must be sourced from Canadian commercial supply after progression.

12.3 Therapy After Protocol Treatment is Stopped

After protocol treatment is stopped, therapy is at the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

Refer to Section 9.2 and Appendices I and IV for details of follow up and required investigations.

Annual minimal follow up using the Short Follow-up Report is required for patients who have not received any protocol therapy. Ineligible patients who have received at least one dose of protocol therapy should be followed as per protocol guidelines outlined in Section 9.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Pathology Review

There will be no central pathology review for this study.

13.2 Tissue Collection

A detailed Correlative Studies Manual will be provided at centre activation, which will include details regarding sample preparation, handling and shipping.

The submission of a representative block of the diagnostic tumour tissue and adjacent normal tissue (part of the standard resection), as well as diagnostic tissue submission at the time of progression (when feasible), is mandatory for participation on this trial. These should be submitted upon request from the Central Tumour Bank.

Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumour from the block) to be substituted as an alternative. Failure to submit any tissue samples as directed will result in the patient being considered ineligible. Where no previously resected or biopsied tumour tissue exists, on the approval of the CCTG, the patient may still be considered eligible for the study.

Blocks will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario. Tumour blocks will be the preferred material to collect, as one of the objectives may be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of breast cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization 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.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to pathology departments for a representative tumour block.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

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

Tumour blocks will be requested by the Queen's Department of Pathology and instructions will be included in the request as to where blocks should be sent. The request will be sent to the person named in the Correlative Studies Report. Please consult the lab manual for additional information.

13.3 Blood Collection

Whole blood will be collected in Streck tubes and processed for the purpose of cell free DNA analysis. This will be collected prior to the start of protocol therapy (pre day 1 – cycle 1) and then every 12 weeks after randomization until relapse/progression, and at the time of relapse/progression. These samples will also be used for the purposed of lymphocyte extraction (baseline sample only). The collection and processing of whole blood for the purposes of collecting circulating tumour DNA is a **mandatory** component of this trial. Failure to submit these samples as directed in section 9 of the protocol, and as per the laboratory manual, will result in the patient being considered ineligible. Please consult the lab manual for details of specimen collection, processing and shipment for this purpose.

Submission of *additional* whole blood, plasma and serum for the purposes of banking/future research is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. These samples will be collected at the same time as the cell free DNA samples, processed at the sites and will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

At the specified times, participants will provide the following blood specimens: STRECK tubes (whole blood in EDTA for cell free DNA extraction), lavender topped tubes (whole blood in EDTA), light green topped tubes (containing lithium heparin - for plasma), and red topped tubes (for serum).

Specimens will be processed and stored at participating centers immediately after collection and then shipped to a central laboratory, frozen on dry ice, in batches of 10 sets or more (1 set = entire blood collection at one patient visit), for subsequent storage and future analysis. Please consult the lab manual for specimen collection and shipping details.

Type of Tube	STRECK Tube (1 x 10mL) (2.1 teaspoons)	Lavender Top Tube (1 x 6 ml) (1.2 teaspoons)	Light Green Top Tubes (2 x 4.5 ml) (1.8 teaspoons)	Red Top Tube (2 x 6 ml) (2.4 teaspoons)
To be used for	Cell free DNA and lymphocyte extraction *(mandatory)*	Whole blood for storage for future research *(optional)*	Plasma for storage for future research *(optional)*	Serum for storage for future research *(optional)*

TOTAL VOLUME DRAWN = 37 ml (7.5 Teaspoons)

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this trial is to estimate the hazard ratio of the progression-free survival for two different dose regimens of palbociclib in combination with endocrine therapy (fulvestrant or tamoxifen or Aromatase Inhibitor) as second line therapy in women with ER positive, HER2 negative, advanced/metastatic breast cancer. Second objectives include comparisons of safety and tolerability, response rate (in patients with measurable disease), duration of response, clinical benefit rate, overall survival between two treatment arms. After stratification by centre, visceral metastases (yes versus no), duration of exposure to most recent endocrine therapy prior to randomization ($\geq$ 6 months versus < 6 months in the advanced/metastatic setting or $\geq$ 24 months versus < 24 months in the adjuvant setting), and planned use of fulvestrant versus tamoxifen versus aromatase inhibitor, patients will be randomized using a minimization method and in a 1:1 ratio to two treatment arms: palbociclib 100 mg po daily + fulvestrant or tamoxifen or AI at the standard doses/schedules (Arm 1) and palbociclib 125 mg po daily 3 out of 4 weeks + fulvestrant or tamoxifen or AI at the standard doses/schedules (Arm 2).

14.2 Primary Endpoints and Analysis

The primary endpoint is progression free survival (PFS) defined as time from randomization to progression or death from any cause. Disease progression will be investigator assessed using the RECIST 1.1 criteria *[Eisenhauer 2009]*. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last disease assessment. All patients randomized will be included in the analysis of PFS. The hazard ratio of Arm 1 to Arm 2 and 90% confidence interval will be derived from a stratified Cox model adjusting for two stratification factors (visceral metastases and duration of exposure to prior endocrine therapy) at randomization. Overall survival, defined as time from randomization to the time when death from any cause is documented, will be analyzed similarly.

Response and clinical benefit rates are defined respectively as proportion of all randomized patients with CR or PR as their best responses or with CR. PR, and SD as their best responses and will be compared between two arms using the Cochran-Mantel-Haenszel test adjusting for two stratification factors (visceral metastases and duration of exposure to prior endocrine therapy) at randomization. For patients with documented CR or PR, duration of response is calculated from the time of CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented or death occurs. If a patient has not progressed or died at the time of the final analysis, duration of response will be censored on the date of the last disease assessment. The difference in duration of response between the two treatment arms will be tested using the log-rank test.

All patients who have received at least one dose of study treatment will be included in the safety and tolerability analysis. A Fisher's exact test will be used as needed to compare toxicities between the two arms.

14.3 Sample Size and Duration of Study

Based on the PALOMA 3 study results, a conservative estimated of PFS for the control arm (125 mg daily, 3/ 4 weeks) is 10 months (Turner 2015).

The objective of this trial is to estimate the relative efficacy between the two arms. It will not include a test of superiority or non-inferiority between the two arms. The sample size is based on estimating the hazard ratio (HR) of two arms (experimental vs. control) within a 90% confidence interval (CI). For a 1:1 randomization with 1 year accrual and one-year additional follow-up. If we observe approximately 58 PFS events in each arm, the upper bound of the 90% CI will be 1.36 times the estimated HR and the lower bound will be 0.74 times the estimated HR. Assuming a median PFS of approximately 10 months for both treatment arms, and duration of accrual and follow-up both at 1 year, and a dropout rate of 10%, the study would need to enroll approximately 90 subjects in each arm. If the observed hazard ratio is 0.736 or less, then the upper bound of the 90% confidence interval will be less than 1.

14.4 Safety Monitoring

Adverse events and their frequencies will be monitored on an ongoing basis by the CCTG Statistics and Operations Office personnel and reviewed by the independent Data Safety and Monitoring Committee on a 6 monthly basis with more frequent evaluation as required. This data will also be presented to the Study Chair, Trial Committee and investigator network at annual investigator meetings.

In addition a detailed safety evaluation will be performed after the initial 12 patients on both arms are enrolled and followed for 8 weeks to assess safety, tolerability and compliance with therapy, including dose reductions and dose discontinuations. Adverse events of importance will include grade 3 or 4 neutropenia, febrile neutropenia, infections and death. Accrual will continue during this safety assessment.

14.5 Interim Analysis

There will be no interim analysis for efficacy.

14.6. Quality of Life Analyses

The EORTC QLQ-C30 and the Trial Specific Checklist will be mandatory. Scoring of questionnaires will be conducted by the central office of CCTG according to the scoring manual of the EORTC QLQ-C30. The Trial Specific Checklist items will be scored individually. QOL results will be described and exploratory analysis will be conducted to compare the QOL between the 2 groups.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

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

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

15.1.2 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)."

15.2 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).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Pfizer, 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.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 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).

16.2 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 enrolment 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.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an 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.

16.3.1 *Obtaining Consent for Pregnancy/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 forms for "Pregnancy Follow-up" and "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 pregnant partner or 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*. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

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

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

16.4 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.

16.5 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.

16.6 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.

16.7 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).

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

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the MA.38 area of the CCTG web-site (www.ctg.queensu.ca).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (within 14 days prior to randomization – unless otherwise specified)	On Treatment (Day 1 of each cycle)	On Treatment (every 12 weeks)	End of Treatment (4 week follow-up visit)	Subsequent Follow-Up Visit (prior to Disease progression	At time of disease progression	Follow-up (following disease progression)
Medical History and Physical							
History	X	X		X	X		X
Concurrent Illnesses	X	X		X			
Concomitant Medication	X	X		X			
Physical exam (height, Weight, Blood Pressure, Pulse and ECOG Performance Status)	X	X		X	X		
Hematology[5]							
CBC	X	X[4]		X			
Differential	X	X[4]		X			
HBA1c	X	X[4]		X			
Biochemistry[5]							
Serum Creatinine	X	X		X			
Bilirubin (total)	X	X		X			
Radiology[6]							
CT/MRI of the chest, abdomen and pelvis	X[2]		X	X	X		
Bone Scan or PET[1]	X[2]	As Clinically Indicated					
Other imaging as necessary to document all sites of disease	X[2]	As Clinically Indicated					
Other Investigations							
Pregnancy Test	X[3]	As Clinically Indicated					
ECG	X	As Clinically Indicated					
Urinalysis	X	As Clinically Indicated					
Ophthalmology Exam	As Clinically Indicated						
Adverse Events							
Continuously graded and recorded according to CTCAE v4.0	X	X		X[11]	X[11]		X[11]
Correlative Studies							
Archival tissue blocks	X					X[10]	
Whole blood for cell-free DNA	X[7]		X[7]		X[7]	X	
Whole blood for lymphocytes	X						
Whole blood for banking	X[8]						
Serum and plasma for banking	X[7]		X[7]		X[7]	X	
Quality of Life							
EORTC QLQ-C30	X	X[9]	X[9]	X[9]	X[9]		
Trial Specific Checklist	X	X[9]	X[9]	X[9]	X[9]		

footnotes on next page …

1	Per Institutional Standard (mandatory for patients with bone only disease at baseline and every 12 weeks from randomization – schedule must be maintained).
2	Within 28 days prior to randomization.
3	Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
4	CBC and differential required every 2 weeks for the first two cycles, and then on day 1 of each cycle thereafter. HBA1c is required day 1 every 3rd cycle (i.e. cycle 3, 6, 9, 12, etc.).
5	Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
6	Every 12 weeks from randomization until progression (CT schedule must be maintained).
7	Mandatory whole blood samples for cell free DNA and optional serum and plasma banking for consenting patients are required to be obtained at the following time points; Baseline and then every 12 weeks from randomization.
8	Optional whole blood banking for consenting patients only. Only required to be obtained at baseline.
9	Required At 4, 8 and 12 weeks and then every 12 weeks until progressive disease.
10	If feasible.
11	Only Adverse Events deemed related to protocol therapy (Palbociclib, Fulvestrant or Tamoxifen or AI).

APPENDIX II - 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 III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Distribution

Palbociclib will be supplied by Pfizer Inc. and distributed by Bay Area Research Logistics (BARL) to participating centres.

Fulvestrant will be supplied for this study, and distributed by Bay Area Logistics (BARL) to participating centres.

All other drugs for this protocol are commercially available and sourced from the Canadian market.

Drug Labelling

Drug supplies for this study will be labelled in accordance with Health Canada regulations.

Initial Drug Supply:

Once a centre is locally activated (following receipt and review of all required documentation), the CCTG will authorize a start-up supply of Palbociclib to be shipped directly to the centre. The drug will be shipped to the centre within 5 working days of local activation. Drug accountability and drug re-order forms will be included with the drug shipment and are also available on the trial website.

Please note that sites must request their initial supply of palbociclib (and fulvestrant) from BARL directly.

Drug Ordering (Re-Supply)

Fax a copy of the re-order form (available on the trial website) to the distributor.

Drug Accountability

The investigational products are to be prescribed only by the investigator and co-investigators 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 of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction

Expired/used study drug may be destroyed as per local standard operating procedures. Destruction of expired/used drug must be documented on the Drug Accountability Log and a copy of the destruction certificate kept on file in the pharmacy. 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. However, study drug may NOT be transferred to pharmacies or physicians outside the participating centre.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the MA.38 area of the CCTG web-site (www.ctg.queensu.ca).

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

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required*
Eligibility Checklist		Within 2 weeks of randomization	Consent form**, relevant pathology report(s), relevant radiology report(s)
Baseline Report		Within 2 weeks of randomization	
Correlative Studies Report (Tumour and Blood)	Continuous running-log folder See sections 6.0 and 9.0	Information pertaining to baseline/pretreatment (i.e. tumour specimen information and blood collection for correlative studies) must be completed within 2 weeks of randomization. Tissue to be submitted immediately upon request.	Consent form** Diagnostic pathology report (for tumour tissue only)
		Information pertaining to post randomization tissue and blood collection samples for correlative studies and banking should be completed within 2 weeks after collection of final blood specimen.	
		Information pertaining to skin/blood collection for Pharmacokinetics/ Pharmacodynamics must be completed in EDC in real-time, as soon as the sample is collected.	
Treatment Report	Every 28 days	Within 2 weeks of the end of the cycle	Relevant radiology reports
End of Treatment Report	End of treatment	Within 2 weeks of the end of treatment	None
Relapse/Progression Report	Upon disease relapse/progression	Within 4 weeks of progression	Relevant radiology and pathology reports
4 Week Follow-up Report	4 weeks from the end of the last cycle	Within 2 weeks of the follow-up visit	Relevant radiology reports
Follow-up Report	Every 12 weeks	Within 4 weeks of the follow-up visit	Relevant radiology reports
Short Follow-up Report	Every 12 weeks	Within 4 weeks of the follow-up visit	None
Death Report	When patient dies****	Within 4 weeks of the patient's death	Copy of post-mortem report if performed
SAE Report***	At time of event	Within 1 working day	None

* Scan and upload into the EDC Supporting Document Upload Tool

** For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.

*** See section 11.0 Serious Adverse Event Reporting for details.

**** It is the investigator's responsibility to investigate and report the date and cause of death of any patient entered into this trial.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

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

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

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

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

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

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

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

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

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

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

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

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

2. Pretreatment Assessment

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

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

3. Assessments During Treatment

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

4. Assessments During Follow-up

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

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

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

5. What If . . .

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

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

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

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

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

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

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

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

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

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

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

6. Waiving the Quality of Life Component

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

7. Unwillingness to Complete Quality of Life Questionnaire

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

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

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

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

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **MA.38**

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

Patient Information

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

Institution: _____ Investigator: _____

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

☐ Prior to randomization

During chemotherapy:

☐ Week 4 ☐ Week 8 ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week48 ☐ Week 60

☐ Week _____

Off Treatment:

☐ Week 4 ☐ Week 8 ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week48 ☐ Week 60

☐ Week _____

** Note: Questionnaire is not required to be completed at time of relapse/new primary malignancy or afterwards.*

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

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

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

Comments: _____

_____

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

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

CCTG use only

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

_____ - ____ - ____ _____ - ____ - ____ _____ - ____ - ____ _____ _____

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

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (MA.38)

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

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

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

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

Please go on to the next page

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

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

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

Please go on to the next page

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

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you have a sore mouth?	1	2	3	4
32. Have you had tingling hands or feet?	1	2	3	4
33. Were your fingers or toes numb (loss of feeling)?	1	2	3	4

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

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

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

Thank you.

APPENDIX VII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

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

APPENDIX VIII - PROHIBITED MEDICATIONS

Drug class	Agent	**Wash-out** (period of time that the medication should be discontinued prior to administration of the first dose of protocol treatment)*
Inducers of CYP3A4		
Antibiotics	All rifamycin class agents (rifampicin, rifabutin, rifapentine)	7 days
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (phenobarbital)	7 days
Antiretrovirals	Efavirenz, nevirapine, tipranivir, etravirine	7 days
Glucocorticoids (oral)	Chronic use of cortisone (> 50mg), hydrocortisone (> 40 mg), prednisone or prednisolone (> 10 mg), methylprednisolone or triamcinolone (> 8 mg), betamethasone or dexamethasone (> 1.5 mg). Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed. Short term steroid use (up to 2 weeks) is allowed**.**	7 days
Other	St. John's Wort, modafinil	7 days
Inhibitors of CYP3A4		
Antibiotic	clarithromycin, erythromycin, troleandomycin, flucloxacillin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (> 150 mg daily), voriconazole	7 days
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir, atazanavir	7 days
Calcium channel blockers	verapamil, diltiazem	7 days
Antidepressants	nefazodone, fluvoxamine	7 days
GI Agents	Cimetidine, aprepitant	7 days
Other	grapefruit, grapefruit juice, seville oranges, star fruit, papaw, amiodarone	7 days
Miscellaneous		
Herbal or dietary supplements and traditional Chinese medicines	Ginkgo biloba, kava, grape seed, valerian, ginseng, *Echinacea*, evening primrose oil.	14 days

* All patients must have observed the specified washout period for all prohibited drugs prior to randomization..

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Sue Steacy Clinical Trials Assistant, CCTG Email: ssteacy@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Chad Winch Study Coordinator, CCTG Email: cwinch@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Anil Abraham Joy Email: anil.joy@ahs.ca	780-432-8762	780-432-8888
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Chad Winch Study Coordinator, CCTG Email: cwinch@ctg.queensu.ca	613-533-6430	613-533-2941
DRUG ORDERING See Appendix III for full details.	See Appendix III and trial website: www.ctg.queensu.ca		