SUMMARY OF CHANGES

NCI Protocol #: 9322
Local Protocol #: PHL-086

Protocol Date: Amendment 12 / 09Feb2018

#	Section	Page(s)	Change
1	Throughout	Throughout	Changed the version date from 19Apr2017 to 09Feb2018. **Rationale:** To update version date.
2	Cover Page	5	Changed Responsible Data Manager name and contact information, from Sukhi Brah to Oulu Zhu. **Rationale:** To update to current Data Manager and contact information
3	Section 6	36	Changes (highlighted text inserted): Grade 4 febrile neutropenia: In this case, upon recovery of ANC to grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval. **Rationale:** To clarify the term of the corresponding AE.
4	Section 7	51-52	Changes (highlighted text inserted, ~~strikethrough~~ text deleted): ENDOCRINE DISORDERS – ~~Endocrine disorders, Other (~~hHypopituitarism~~)~~ GASTROINTESTINAL DISORDERS – ~~Gastrointestinal disorders, Other (~~aAnal fissure~~)~~ INVESTIGATIONS – ~~Investigations, Other (~~bBlood lactate dehydrogenase increased~~)~~; ~~Investigations, Other (eosinophil count increased~~ Eosinophilia~~)~~; ~~Investigations, Other (glucose urine present~~ Glucosuria~~)~~ MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – ~~Musculoskeletal and connective tissue disorders, Other (~~oOsteonecrosis~~)~~; ~~Musculoskeletal and connective tissue disorders, Other (~~rRhabdomyolysis~~)~~ NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) – ~~Neoplasms benign, malignant and unspecified (incl cysts and polyps), Other (~~tTumor hemorrhage~~)~~ NERVOUS SYSTEM DISORDERS – ~~Nervous system disorders, Other (~~sSpinal cord compression~~)~~ RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – ~~Respiratory, thoracic and mediastinal disorders, Other~~

			~~(o~~Oropharyngeal pain~~)~~ **Rationale:** Adverse event terms updated based on CTCAE 5.0.
5	Throughout Section 7.1	Throughout 52-54	Changed the version date of CTCAE from v 4.0 to v 5.0. Changes (highlighted text inserted, ~~strikethrough~~ text deleted): **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized ~~for AE reporting~~ until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0~~4.0~~. A copy of the CTCAE version 5.0~~4.0~~ can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. **Rationale:** CTCAE version has been updated as per CTEP request letter dated 12-Jan-2018
6	Section 7.2.1	53	Changes (highlighted text inserted): https://ctep.cancer.gov **Rationale:** Links to CTEP Website updated as the previous address did not work.

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TITLE: A Phase 2 Study of XL184 (Cabozantinib) in Recurrent or Metastatic Endometrial Cancer

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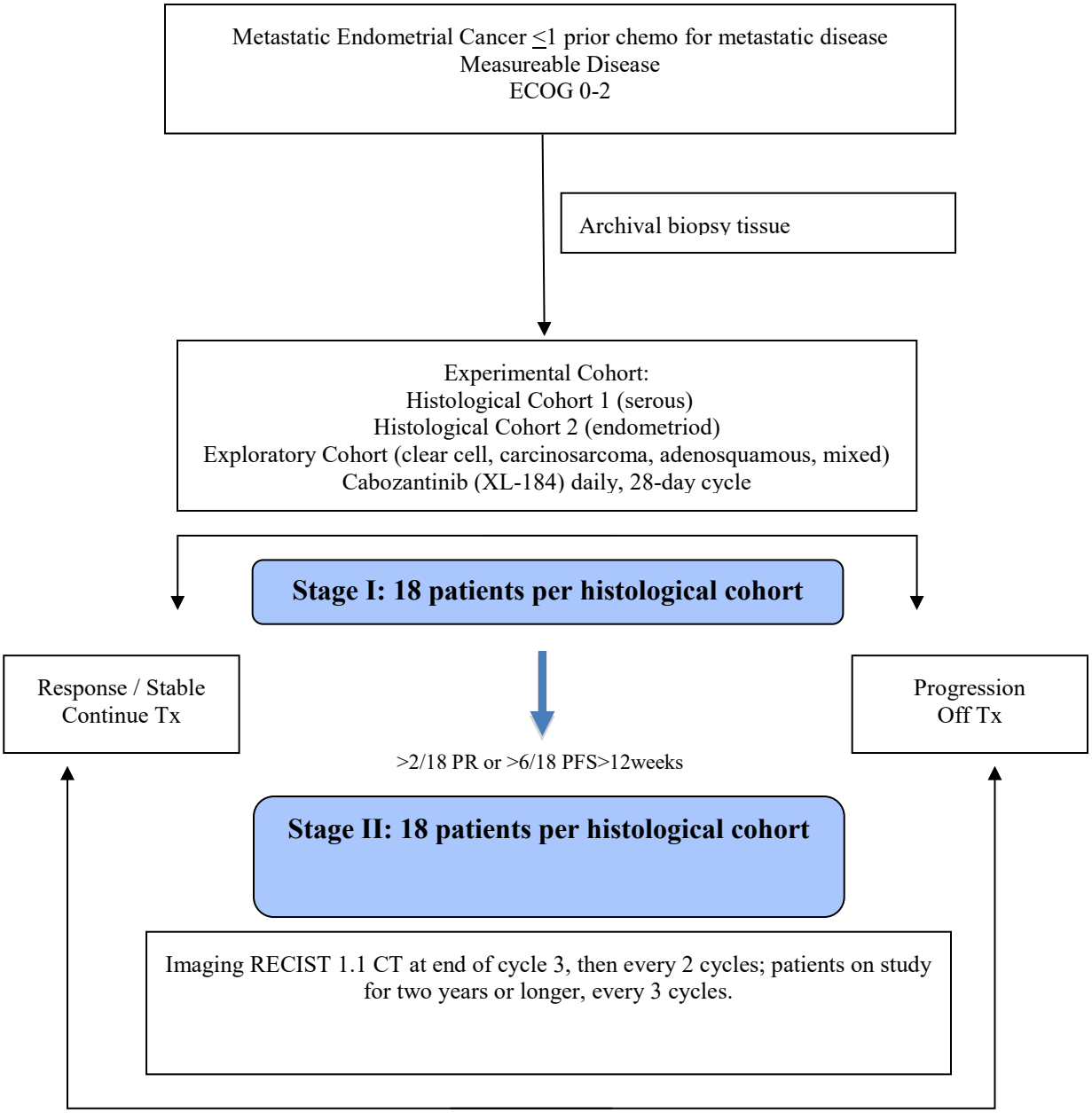
NCI Supplied Agent: XL184 (cabozantinib) (NSC # 761968; IND # 116059)

Protocol Date: Initial / 20November2012
Amendment 1/ 29April2013
Amendment 2/ 27Aug2013
Amendment 3/ 28January2014
Amendment 4 / 14April2014
Amendment 5/ 15September2014
Amendment 6/ 12Aug2015
Amendment 7/ 23February2016
Amendment 8/11May2016
Amendment 9/14Dec2016
Amendment 10/10Feb2016
Amendment 11/19Apr2017
Amendment 12/09Feb2018

SCHEMA


Metastatic Endometrial Cancer ≤1 prior chemo for metastatic disease
Measureable Disease
ECOG 0-2
Archival biopsy tissue
Experimental Cohort:
Histological Cohort 1 (serous)
Histological Cohort 2 (endometriod)
Exploratory Cohort (clear cell, carcinosarcoma, adenosquamous, mixed)
Cabozantinib (XL-184) daily, 28-day cycle
Stage I: 18 patients per histological cohort
Response / Stable
Continue Tx
Progression
Off Tx
>2/18 PR or >6/18 PFS>12weeks
Stage II: 18 patients per histological cohort
Imaging RECIST 1.1 CT at end of cycle 3, then every 2 cycles; patients on study for two years or longer, every 3 cycles.

Study Summary

This is a single arm phase II study to evaluate the activity of the multi-targeted inhibitor cabozantinib (with activity against MET, VEGFR2, TIE2, RET, AXL and KIT) in endometrial cancer (with a dual primary endpoint of improved response rate and 12-week progression-free-survival (PFS)). Cabozantinib co-mines the simultaneous targeting of epithelial cell growth factor signaling and angiogenic support from stromal compartments. Correlative studies include evaluation of mutational profiles and met amplification status as baseline molecular predictors of response.

Eligible patients include those with serous or endometroid histology endometrial cancer with radiographic disease progression after one line of cytotoxic therapy for metastatic disease or with progression within 12 months of completing adjuvant chemotherapy. Chemotherapy and radiation administered in the adjuvant setting will be allowed as well as prior hormonal manipulation. In addition, a separate cohort of patients with unusual histology endometrial cancer (including clear cell, carcinosarcoma) will also be accrued applying same eligibility criteria. The statistical plan to assess efficacy will only apply to the experimental cohort (serous and endometroid histology patients).

Dosing of cabozantinib will be continuous (7 days a week) on a 28 day cycle, with response evaluation performed, at the end of cycle 3, then every 2 cycles with CT tumour measurements by RECIST (Study Schema).

Statistical plan is based on efficacy in serous and endometroid histology endometrial cancer. A modified Simon two-stage design is planned with a maximum accrual of 36 patients per histological cohort (i.e. 72 patients in total) to discriminate between co-primary endpoints of tumor response rates of 30% vs. 10% and 12-week progression-free-survival (PFS) rates of 55% vs. 30% (corresponding to median PFS of 3.4 vs. 1.7 months). Stage I has a planned accrual of 18 patients per histological group. If no more than 2 objective responses (no more than 11%), and no more than 6 instances of 12-week PFS (no more than 33%), are observed among the initial 18 patients, that cohort would be terminated early and declared negative but the other cohort can continue to accrue and will be analyzed separately. Otherwise study will proceed to Stage II accrual to a maximum of 36 patients per histological cohort. If at least 8 objective responses (at least 22%), or at least 16 instances of 12-week PFS (at least 44%) are observed among the 36 evaluable patients, this agent would be considered worthy of further testing in that particular histological subgroup of endometrial cancer.

Adverse events will be graded using CTCAE v 5.0.

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1. OBJECTIVES

1.1 Primary Objectives

Determine efficacy of single agent cabozatinib in women previously receiving one line of chemotherapy for metastatic endometrial cancer or with progression within 12 months of completing adjuvant therapy, with co-primary endpoints of

- objective response rate by RECIST 1.1
- progression-free-survival at 12 weeks (PFS)

1.2 Secondary Objectives

Correlation of clinical response with:

- baseline molecular status of archival tumour (c-met amplification & mutation status)
- overall survival

2. BACKGROUND

2.1 Endometrial Cancer: Epidemiology and Contemporary Management

Endometrial cancer is the highest incidence gynecologic malignancy and remains the 4th most common cancer diagnosis in North American women less frequent only to diagnoses of breast, lung and colorectal cancer. In 2012, approximately 5600 more women will be diagnosed with, and 900 will die of this disease in Canada. US statistics parallel those of Canada with an approximately 10-fold difference [1, 2].

The main risk factor for the development of endometrial cancer continues to be prolonged exposure to unopposed estrogen. Other identified risk factors (nulliparity, use of taxomifen, hormone replacement therapy etc) are likely relevant due to the pathology-promoting imbalance of estrogen/progesterone they create. The ever growing obesity epidemic with its consequent metabolic syndromes is yet another factor promoting estrogenic imbalances in women and is likely a major contributing factor to the burden of disease we currently see related to endometrial cancer.

Uterine cancer is predominantly a disease of older women who present with aberrant post-menopausal bleeding as the first symptom of their disease. The majority of women are diagnosed with early stage disease and have a relatively good prognosis, with 5-year disease-free survivals of greater than 80%. Surgery continues to be the mainstay of management; however both chemotherapy and radiation have demonstrated utility at reducing the risk of local and distant disease recurrence and have now become standard practice. Unfortunately a not insignificant percentage of women with early stage disease are at a greater risk of developing disease recurrence. Factors like age > 60, depth of invasion, involvement of lower uterine segment, non-endometroid histology and the presence of lymphovascular invasion or aneuploidy, have demonstrated importance in identifying those at a particularly high risk of failing primary

therapy [3, 4]. These women, together with those with more advanced disease at initial presentation have a relatively poor prognosis, and in contrast with the high 5-year disease free survival in early stage disease, women with stage IV disease can expect about a 20% chance of the same. There is significant heterogeneity within this group as patients with endometroid histology cancer tend to have more slow-growing disease that may respond to hormonal manipulation while patients with high grade serous cancers follow a more aggressive course and benefit from a limited number of cytotoxic therapies. The best responses are to agents like doxorubicin and cisplatin which are still modest and in the range of 20 to 40% and where noted are transient in duration [3, 5]. Although combination regimens have demonstrated higher response rates, given their increased toxicities and unclear impact on survival their use in the palliative setting of these patients is unclear [6].

2.2 **Relevance of Histopathology and Molecular Characterization**

Endometrial cancers encompass a broad range of tumour histologies. The majority of patients close to 80%, are diagnosed with endometroid adenocarcinomas also known as Type I cancers. These are the traditional uterine cancers characterized by low grade histology and a relatively indolent course, developing in older women possessing the standard risk factors associated with unopposed estrogen excess and responsive to therapeutic hormonal manipulation. The Type II or non-endometroid histology endometrial cancers follow a very different clinical course. The most common histology in this uncommon group is the serous histology cancers which in spite of being considered in a similar context to serous ovarian cancers, have demonstrated an inferior clinical course matched stage-for-stage. This group also includes clear cell, carcinosarcoma and stromal sarcomas albeit at much lower frequencies all with their own unique clinical and molecular profiles. In spite of comprising a small proportion of all uterine cancers, non-endometroid histology cancers account for about 50% cases of recurrent disease and therefore represent a significant management challenge [3].

Apart from their distinctive clinical trajectories, the different histologies of endometrial cancer also have somewhat divergent molecular backgrounds suggesting a dualistic model of endometrial carcinogenesis that is especially relevant in the context of developing rationale targeted therapies and combinations thereof. Endometroid cancers tend to be low grade (grade 1) occurring on a background of atypical complex hyperplasia. They express both estrogen (ER) and progesterone (PR) receptors and demonstrate loss of PTEN tumour suppressor gene (with uninhibited activation of the PI3K/Akt pathway), mutation in KRAS and defects in DNA damage mismatch repair pathways. Serous endometrial cancers are exclusively high grade arising on a background of atrophy, tend to be non-diploid karyotype, ER/PR negative and demonstrating loss of p53 and activation of Her2/neu [3]. Molecular profiles of clear cell and carcinosarcoma have been less well evaluated and these appear to be a somewhat heterogenous group of diseases in their own right [7].

Given the heterogeneity inherent in this patient population with respect to both clinical course and therapeutic response, there is optimism that novel approaches aimed specifically at differential vulnerabilities within different molecular subgroups of this disease will improve outcomes for patients with endometrial cancer. [8]

2.3 **XL-184 (Cabozatinib)**

Characterization of XL-184 and rationale for HGF targeting in cancer

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2011). The primary targets of XL184 are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of XL184 against c-Met and VEGFR2 has been demonstrated in preclinical and clinical studies.

RTKs regulate numerous processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair [9]. Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have all been implicated as causative factors in the development and progression of numerous human cancers. The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) [9]. c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (e.g., renal tubular cells, gland formation, etc.), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells in vitro and metastases in vivo (Investigator's Brochure, 2011). c-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) Overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) Correlation of receptor and ligand overexpression with disease severity and outcome; (3) Genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) Introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorgenicity and metastatic propensity on engineered cells; (5) Introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) Inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (e.g., NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo [9].

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity [10], either by means of c-Met kinase overexpression [11]; activating c-Met gene mutations and/or amplification [11-13]; or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF [14, 15]. These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis [14].

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability [16]. Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer [17]. High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (i.e., therapy-resistant) breast cancer and poor survival.

Nonclinical Development of XL184

In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes et al., 2009). In RIP-Tag2 transgenic mice, tumors treated with XL184 were smaller ($P < 0.05$) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive ($P < 0.05$) and had no liver metastases [18]. All mice treated with XL184 ($n = 6$) survived until 20 weeks, but none treated with vehicle ($n = 14$) or anti-VEGF antibody ($n = 8$) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days [19]. Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg [20]. XL184 increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, XL184 disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors ($P < 0.001$) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses ($P < 0.01$), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, XL184 inhibited tumor growth ($P < 0.001$) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, $P < 0.0001$) when compared with predose tumor weights. Subchronic administration of XL184 was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone [21] (Zhang et al., 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2011). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 treated animals appeared mostly

normal. Thus, XL184 treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED50) of targets was achieved at well tolerated doses of XL184 and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2010). XL184 produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of XL184. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, i.e., inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of XL184 resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg, [22]. Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met [20]. This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy [22]. In rats, plasma concentrations in the range of 5 to 15 μM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 μM were observed at highly efficacious doses in mice. These results were consistent with in vivo target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2010). In rats, the oral bioavailability of XL184 dosed as a solid was approximately 100% of XL184 dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [Cmax] and area under the time-concentration curve from 0 to t hours post-dose [AUC0-t] values) associated with single XL184 oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) [22]. With repeat daily oral dosing in rats, systemic exposure (AUC0-t values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The Cmax and AUC0-t values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to XL184 in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (Cmax and AUC0-t values) associated with single XL184 oral doses in dogs increased less than dose-proportionally with increasing XL184 dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption [23]. With repeat daily dosing, exposure (Cmax and AUC0-24 values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

Toxicology

In rodents and non-rodents, histopathological changes associated with XL184 administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues [23]. Histopathological changes present in the bone and pancreas were considered secondary to XL184 administration. Adverse effects following oral exposure to XL184 were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, XL184 administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg XL184 capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 was negative in an S. typhimurium / E.coli bacterial mutagenicity study, an in vitro chromosome aberration study using human peripheral blood lymphocytes, and an in vivo mouse bone marrow micronucleus study (Investigator's Brochure, 2010). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184-treated rats or on cardiovascular function in XL184-treated dogs.

Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with XL184 treatment 1) as a single agent at does ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2011). Safety and efficacy information, from the 2011 Investigator's Brochure, is summarized below.

Phase I Studies

Study XL184-001 was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) to 265 qd were enrolled. Capsule dose levels were 175mg qd and 250mg qd (using capsules [25 and/or 100mg] for two, 14-day cycles). The capsule MTD was determined to be 175 mg qd (Kurzrock et al., 2011). Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of ≥30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

In Study XL184-002, treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2011 Investigator's Brochure. All adverse events (AEs) were assessed with respect to combination treatment and not the individual components. Nineteen patients were evaluated for AEs, the most common grade 3 or higher included neutropenia (21%), thrombocytopenia (16%), leucopenia (16%), and hypertension (11%). Myelosuppression, including prolonged pancytopenia, is a dose-limiting toxicity (DLTs) associated with TMZ use. The frequency at which bone marrow toxicity was observed in this study is consistent with the TMZ prescribing information.

Study XL184-004 is a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules 30 minutes after administration of a high fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules under fasting conditions). Blood samples were collected up to 504 hours post dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics. See "Pharmacokinetics" section for results.

Study XL184-005 is a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100 mg tablet) or Reference (100 mg cabozantinib, dosed as two 50 mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post dose for each subject after each treatment to assess plasma cabozantinib PK. See "Pharmacokinetics" section for results.

In Study XL184-008, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase 1 study, CA205-001, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. Because of a change in study sponsor, this study was reinitiated as XL184-014. One additional subject was enrolled as of May 2011 at 50 mg PO qd.

Study XL184-202 was a phase 1b/2 trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase 1 dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A cPR was observed in 5 subjects (8%) and 24 subjects (37%) had SD/PR ≥4 months. The most common grade 3 or higher AEs in the phase 1 portion included diarrhea (44%), fatigue (22%), hypokalemia (11%), decreased appetite (6%), dyspnea (14%), lipase increase (6%), hypomagnesemia (6%), and dehydration (5%). Twenty-eight subjects were enrolled in the phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced progressive disease (PD), received single-agent cabozantinib or cabozantinib with erlotinib. AEs ≥grade 3 included dehydration (8%) and hypertension (8%). One patient, who was treated with single-agent cabozantinib, had a cPR.

Phase 2 Studies

In a phase 2 study, XL184-201, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal related.

Study XL184-203 is a phase 2 randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric / gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal related SAEs.

Study XL184-205 is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3), and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Phase 3 Studies

Study XL184-301 is a blinded, randomized control trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in

Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Adverse Events

The clinical studies with XL184 are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with XL184 (806 in single-agent studies and 107 in combination studies of XL184 with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2011). Data from the 806 subjects who received single-agent XL184 show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination XL184 studies. The most commonly reported SAEs that were assessed as related to study treatment with XL184 (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

There have been 15 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), PE (two subjects), respiratory failure (two subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (two subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), hemorrhage (presumed to be hemoptysis; one subject), and diverticular perforation, peritonitis (one subject) (Investigator's Brochure, 2011).

Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial XL184-001 showed dose proportional increases in maximum plasma concentration (Cmax) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 175 and 250 mg qd) (Kurzrock, 2011). Terminal-phase half-life (t1/2,z) values were 59.1 to 136 hours (Investigator's Brochure, 2011). After repeat dosing, t1/2,z values (mean ± standard deviation) for XL184 were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by Day 15 (Kurzrock, 2011). Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Patients who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 (7.68 ± 2.85 mcg·h/mL; n = 23 vs. 41.6 ± 15.3 mcg·h/mL; n = 23), indicating that XL184 accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in XL184-005 who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal t1/2, z of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (tmax) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for Cmax and the area under the plasma drug

concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% Cmax: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [AUC0-last or AUC0-inf]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean Cmax of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean AUC0-last and AUC0-inf values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial XL184-004, a high fat meal did not appear to alter the terminal t1/2, z of cabozantinib [mean t1/2, z : 131 hours (fed) vs 128 hours (fasted)]. The high fat meal significantly increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib Cmax and AUC values by 39% and 56%, respectively. The geometric mean ratio of Cmax fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of AUC0-last fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hour before and 1 hours after each cabozantinib dose).

2.4 **Rationale for Targeting HGF and Angiogenesis in Endometrial Cancer**

Endometrial cancers are a heterogeneous group that can be separated into two distinct histological sub-types with differing molecular backgrounds. The more common endometriod cancers are characterized by aberrant PI3K/PTEN/AKT pathway activation as a consequence of oncogenic mutation of PI3K, PTEN loss and over-expression of upstream growth factor receptors. Serous cancers on the other hand, harbour mutations in p53 and p16 with consequent cell-cycle dysregulation. A subset of these also demonstrates up-regulation of PI3K signaling through gene amplification and oncogenic mutation. Also noteworthy is abnormal regulation of growth factor (HER2, EGFR) and MAPK signalling, the latter via KRAS mutation, specifically in endometroid cancers [8].

It is increasingly evident that focused inhibition of single oncogenic pathways is of limited utility in genetically complex tumours where molecularly driven escape and resistance mechanisms emerge under the selection pressure of isolated pathway inhibition. Consequently, targeting multiple arms of a network (either through combination therapies or multi-targeted agents) has become the recent focus of drug development [24] . In addition, the recognition of the importance of cellular and physical features of the tumoral microenvironment in cancer progression has identified further targets for a multi-pronged approach to tumour targeting [25].

The prognostic importance of microvascular density (MVD) in predicting for advanced disease stage and inferior patient outcome in endometrial cancer lends credence to targeting angiogenic pathways in this disease [26, 27]. It is a particularly appealing therapeutic strategy as it involves simultaneous inhibition of mitogenic pathways in malignant epithelial cells and of paracrine support from the stromal compartment [28]. Since multiple molecular pathways have been implicated in the promotion of angiogenesis the findings of Wagatsuma correlating high MVD with diffuse membranous c-MET expression are interesting and suggest a potential relevance of

hepatocyte growth factor (HGF) – MET molecular cross-talk in promoting tumoral angiogenesis in endometrial cancer [29]. Preclinical work in a variety of in vivo tumour models supports a potentiation of antiangiogenic strategies through contemporaneous inhibition of MET and VEGF RTK pathways [19, 30, 31].

c-MET is a RTK for which the only known ligand is HGF. Ligand binding promotes receptor activation and downstream signalling through MAPK and PI3K, influencing a number of processes integral to malignant progression including growth, motility, invasion and angiogenesis [32]. Over-expression of the MET receptor has been reported in a variety of cancers, and leads to increased paracrine and autocrine signalling through increased sensitivity to stroma produced HGF [33]. Similar findings have been demonstrated in endometrial cancer (in endometroid and serous subtypes) where increased tumour expression of MET and stromal reactivity for HGF correlated with more aggressive tumour biology and inferior patient outcome [29, 34].

Unfortunately, clinical benefit across tumour types from isolated VEGF-pathway targeting strategies has been modest at best and transient in duration[35] . In situations where treatment results in an initial response followed by progression it is likely that acquired mechanisms of resistance related to alternative molecular pathways promoting angiogenesis and tumour progression are the cause. Multiple molecular mediators have been implicated in this regard including FGF (fibroblast growth factor), ephrins, angiopoietins and HGF. Preclinical work also suggests that these mechanisms may also be relevant to the increased metastatic potential noted with VEGF-targeting [36]. It has been suggested that either through targeting of multiple pathways or initiating inhibition of compensatory pathways at the emergence of resistance may result in greater clinical efficacy [37, 38].

The recently reported Phase II trial of single agent bevacizumab in endometrial cancer is one such example. Although activity level was encouraging with a response rate of 13% and a 40% 6-month PFS, these responses were transient. Benefit was noted in all histological subgroups. Interestingly, although tumour VEGF-A levels did not predict for response, circulating levels of the same cytokine seemed to correlate with poor outcome on trial. What remains unclear is whether the lack of discrepancy is related to the use of archival tumour or a true lack of correlation [39].

Current data implies that dual targeting of VEGFR2 and MET signaling, as can be achieved with the multi-targeted tyrosine kinase inhibitor cabozatinib, is likely to result in significant clinical efficacy in endometrial cancer where high levels of angiogenesis and aberrant proliferation pathways are relevant.

Targeting angiogenic pathways has emerged as an attractive therapeutic strategy in endometrial cancer given the prognostic relevance of micro-vascular density (and hence heightened angiogenic activity) in this disease [26, 27, 40]. The results of the recently reported endometrial bevacizumab trial are in accordance with this hypothesis. In women previously receiving cytotoxic treatment for advanced disease, the VEGF monoclonal antibody had a response rate of 13.5%, with 40% women remaining progression-free for at least 6 months [39]. Still, benefit from VEGF targeting strategies is generally transient due to alternate angiogenic pathways and

stromal elaboration of soluble factors [28, 38]. In this regard, two independent studies have suggested relevance of hepatocyte growth factor (HGF) signaling and angiogenesis in endometrial cancer, demonstrating increased expression of HGF's cognate receptor c-MET, in around 60% of endometroid and serous cancers. Further, upregulated c-MET/HGF correlated with aggressive tumour biology and inferior patient survival [29, 34]. From a mechanistic standpoint, preclinical experimental work demonstrates efficacy of HGF-MET targeting through inhibition of both mitogenic and angiogenic tumoral pathways [41].

Study Hypothesis

This is a single arm phase II study to evaluate the hypothesis that the multi-targeted inhibitor cabozantinib (with activity against MET, VEGFR2, TIE2, RET, AXL and KIT) will demonstrate significant activity across various histologies of endometrial cancer (with a dual primary endpoint of improved response rate and 12-week progression-free-survival (PFS)). Efficacy of this approach is likely to be related to the simultaneous targeting of epithelial cell growth factor signaling and angiogenic support from stromal compartments. Exploratory correlative studies are incorporated to evaluate the predictive potential of archival mutational profiles (including c-met amplification status).

2.5 Correlative Studies Background

Rationale for HGF/MET pathway biomarkers

Oncogenic MET signaling is a consequence of various molecular mechanisms including gene amplification, mutation, over-expression, and autocrine activation, with the hierarchal relevance dictated by the tumour context. In addition, downstream HGF-MET signaling is complex and involves several networks that are already aberrantly regulated in human cancers including (but not limited to) PI3K/Akt and RAS-RAF-MEK-ERK. Therefore, molecular markers indicative of (1) the type of pathway aberration, (2) the mutational context of a patient's tumour or (3) the activation status of downstream signaling mediators, may indicate dependence on MET pathway, potentially acting as biomarkers of response to cabozantinib/XL-184.

Overview of correlative studies

Correlative studies evaluating tumour biology relevant to endometrial cancer will focus on baseline amplification status of MET tumour mutational profiling using a custom panel to assess a large panel of cancer-associated mutations as well as baseline status of met amplification.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic endometrial cancer. Eligible histologies for the experimental cohort are: endometroid or serous Eligible histologies for the exploratory cohort are: carcinosarcoma, clear cell, mixed, adenosquamous and any other rare sub-type of endometrial cancer

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥10 mm with CT scan, MRI, or calipers by clinical exam and ≥ 15 mm in short axis for nodal lesions. See Section 11 for the evaluation of measurable disease. Patients must have radiographic evidence of disease progression following the most recent line of treatment.

3.1.3 Prior therapy: Eligible subjects must have had 1 line of systemic cytotoxic treatment. This may be adjuvant therapy with documented progression within 12 months of completion, or 1 line of cytotoxic therapy for metastatic disease.
NOTE: Eligible patients are allowed up to 2 lines of systemic cytotoxic treatment, of which only 1 line is allowed for metastatic disease. The acceptance of progression within 12 months of adjuvant is part inclusion to not require patient to re-challenge with chemo if they progressed soon after adjuvant therapy. Prior hormonal therapy for metastatic/recurrent disease is also allowed. Prior targeted therapy not directed against cMET or VEGF pathways is allowed.

3.1.4 Age ≥18 years on day of consent. As no dosing or adverse event data are currently available on the use of *XL-184* in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Patients must have normal organ and marrow function ≤ 7 days before the first dose of study treatment as defined below:

- absolute neutrophil count ≥1.5 x 10^9/L
- platelets ≥ 100 x 10^9/L
- total bilirubin ≤1.5 × ULN
- AST(SGOT)/ALT(SGPT) ≤3.0 X institutional upper limit of normal
- creatinine ≤ 1.5 × ULN

OR

- creatinine clearance ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- hemoglobin ≥ 90g/L
- serum albumin ≥ 28g/L
- lipase < 2.0 × ULN; no radiologic/clinical evidence pancreatitis
- urine protein / creatinine ratio (UPCR) ≤1
- serum phosphorus, calcium, magnesium and potassium ≥ LLN

3.1.8 Women of childbearing potential must have a negative pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal

ligation, or bilateral oophorectomy) or are not postmenopausal. Postmenopausal is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression or any other reversible reason.

3.1.9 The effects of XL184 on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors agents are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (see below) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

Sexually active subjects must agree to use medically accepted barrier methods of contraception (*e.g.*, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s).

3.1.10 Patients must consent to analysis on archival tissue; if archival sample is not available, a sufficient tumour biopsy can be performed a minimum of 28 days prior to start of treatment if felt to be clinically reasonable.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 **Exclusion Criteria**

3.2.1 Patients who have had chemotherapy (including investigational cytotoxic chemotherapy), biologic agents (*e.g.*, cytokines or antibodies) or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) before the first dose of study treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Prior treatment with cabozantinib.

3.2.3 The subject has received radiation therapy:
- to bone metastasis within 14 days before the first dose of study treatment
- to any other site(s) within 28 days before the first dose of study treatment.

3.2.4 The subject has received radionuclide treatment within 6 weeks of the first dose of study treatment.

3.2.5 The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 14

days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment.

3.2.6 The subject has received any other type of investigational agent within 28 days before the first dose of study treatment.

3.2.7 The subject has not recovered to baseline or CTCAE ≤ Grade 1 from related toxicity to all prior therapies except alopecia and other non-clinically significant AEs.

3.2.8 Any other prior malignancy from which the patient has been disease free for less than 3 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of any site or any other cancer.

3.2.9 Patients with known brain metastases should be excluded from this clinical trial.

3.2.10 The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN ≤ 7 days before the first dose of study treatment.

3.2.11 Therapeutic anticoagulation with warfarin, antiplatelet agents (e.g., clopidogrel), thrombin, or Factor Xa inhibitors is not allowed. Therapeutic anticoagulation with low molecular weight heparin (LMWH) is allowed as well as prophylactic anticoagulation using low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and LMWH.

3.2.12 The subject requires chronic concomitant treatment of strong CYP3A4 inducers (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/ ; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.13 The subject has experienced any of the following:

- clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment
- hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment
- any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment

3.2.14 The subject has tumor in contact with, invading or encasing any major blood vessels.

3.2.15 The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.

3.2.16 The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

1. Cardiovascular disorders including:
   a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
   b) Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment
   c) Any history of congenital long QT syndrome
   d) Any of the following within 6 months before the first dose of study treatment:
      - unstable angina pectoris
      - clinically-significant cardiac arrhythmias
      - stroke (including TIA, or other ischemic event)
      - myocardial infarction
      - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)

2. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
   a) Any of the following within 28 days before the first dose of study treatment
      - intra-abdominal tumor/metastases invading GI mucosa
      - active peptic ulcer disease,
      - inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
      - malabsorption syndrome
   b) Any of the following within 6 months before the first dose of study treatment:
      - abdominal fistula
      - gastrointestinal perforation
      - bowel obstruction or gastric outlet obstruction
      - intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment.

3. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy

4. Other clinically significant disorders such as:

a) active uncontrolled infection requiring intravenous systemic treatment within 14 days before the first dose of study treatment
b) serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment
c) history of organ transplant
d) concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment
e) history of major surgery as follows:
    i. Major surgery within 3 months of the first dose of cabozantinib if there were no wound healing complications or within 6 months of the first dose of cabozantinib if there were wound complications
    ii. Minor surgery within 1 month of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications

In addition, complete wound healing from prior surgery must be confirmed at least 28 days before the first dose of cabozantinib irrespective of the time from surgery

3.2.17 The subject is unable to swallow tablets.

3.2.18 The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms ≤ 7 days before the first dose of study treatment.

3.2.19 The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

3.2.20 History of allergic reactions attributed to compounds of similar chemical or biologic composition to XL184

3.2.21 Pregnant women are excluded from this study because XL184 is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with XL184, breastfeeding should be discontinued if the mother is treated with XL184.

3.2.22 Known HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with XL184. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure

differences in intervention effects. The population of Southern Ontario is ethnically diverse. The proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

The population demographics and distribution of minorities in Southern Ontario is included in the following table:

Table: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		**Alberta**		**Ontario**		**Nova Scotia**		**Total**	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20%	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13%**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22%	329,925	11%	2,153,045	19%	34,525	4%	3,353,936	**18%**

Source: Statistics Canada, Census of Population.

Data (2004) from our consortium has been compiled regarding the representation of minorities on previous clinical trials, and the distribution is as follows:

Population Percentage of Minority and Gender of entering PMHC Trials			
	2002	2003	2004
Visible Minorities			
Black	3.6	0	2.8
Asian	7.2	9.0	8.4
Hispanic	2.4	3.0	1.7
Total	**13.2**	**12**	**12.9**
Women	**44.6**	**49.3**	**46.9**

4. REGISTRATION PROCEDURES

4.1 General Guidelines

The Study Coordinator at the Princess Margaret Hospital Consortium Central Office will enter eligible patients on study centrally. All sites should call the Study Coordinator (listed on cover

page) to verify cohort availabilities. The required forms (Eligibility Checklist) will be provided upon site activation.

Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator (cc the central office study coordinator). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. A participating site may order agents only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.2 **Registration Process**

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the PMH Phase II Consortium Central Office. The eligibility checklist will only be sent once this has been received.

No patient can receive protocol treatment until registration with the Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Central Office prior to registration.

To register a patient, the following documents are to be completed by the research nurse or data manager and sent / faxed to the Central Office Study Coordinator:
- Signed patient consent form
- Eligibility Checklist CRF signed by the investigator

To complete the registration process, central office will review the checklist and once eligibility has been confirmed:
- Assign a patient study number
- Assign the patient a dose
- Register the patient on the study
- Fax or e-mail the confirmation worksheet with the patient study number and dose to the participating site

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the study coordinator listed on the front sheet. Patient registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the central office will be closed.

5. TREATMENT PLAN

This is a single agent, two stage non-randomized phase II clinical trial in women with recurrent or metastatic endometrial cancer. Patients will be accrued in two cohorts – experimental, and

exploratory. The study is powered to evaluate efficacy in two histological strata (of serous and endometroid) of endometrial cancer as outlined in statistical plan.

A second exploratory cohort of patients with unusual histology endometrial cancer (including clear cell, carcinosarcoma, mixed) will be accrued to a maximum of 30 patients. Response assessment will be by RECIST and > 4/10 objective responses in a particular histology (if available depending on accrual) will be considered a signal of activity in that particular subtype. Correlative studies are proposed to further elucidate unique features of tumour biology in these rare sub-types.

5.1 **Agent Administration**

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 XL184

XL184 will be dosed continuously (once daily) on a 28 day cycle starting at 60mg daily dose. Skipped/missed doses will not be made up. Patients will undergo their first response evaluation after 3 cycles (12 weeks) of treatment (irrespective of missed/held dose).

Dose Level	Cabozantinib/XL184
1	60 mg daily
-1	40 mg daily
-2	20 mg daily

XL184 must be taken on an empty stomach. Patients must fast for 2 hours before and 1 hour following each dose of XL184.

Patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

5.2 **General Concomitant Medication and Supportive Care Guidelines**

Because there is a potential for interaction of XL184 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.2.1 Concomitant Medications and Therapies

5.2.1.1 Anticancer Therapy

If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (*e.g.*, palliative radiation) are allowed to continue to receive study treatment at the PMHC investigator's discretion.

5.2.1.2 Other Medications

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution.

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically prior to the first dose of study treatment.

No concurrent investigational agents are permitted.

5.2.1.3 Potential Drug Interactions

Cytochrome P450: Preliminary data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (*i.e.*, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from in vitro studies using CYP-isozyme specific neutralizing antibodies.

Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The

chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib (*e.g.*, chronic use of modafinil) should be avoided because of its potential to reduce cabozantinib exposure. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (*e.g.*, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Because in vitro studies only assessed the metabolizing capacity of the CYP3A4, CYP2C9, and CYP2D6 pathways, the potential for drugs that inhibit/induce other CYP450 pathways (*e.g.*, CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007; *http://medicine.iupui.edu/clinpharm/ddis/*).

Protein Binding: Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (*e.g.*, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Drugs Associated with QTc Prolongation: Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see www.crediblemeds.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

Other Interactions: In a relative bioavailability study in dogs, cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Co-administration of gastric pH modifying drugs such as PPI, H2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is now allowed. (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib).

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure.

5.3 **Duration of Therapy**

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Necessity for treatment with other anticancer treatment prohibited by the protocol,
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (*e.g.,* male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment,
- Women who become pregnant or are breast feeding,
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol, or
- Significant noncompliance with the protocol schedule in the opinion of the investigator.
- The minimum dose of study treatment will be 20 mg daily. Subjects who cannot tolerate 20 mg daily will have study treatment discontinued.

5.4 **Duration of Follow Up**

		Follow-Up Period		
		Every 4 weeks (after the end of treatment visit), until disease progression*, up to 12 weeks	Adverse Events to be followed every 4 weeks**	Every 6 months until death***
Reason Patients removed from study:	Disease progression		X	X
	Unacceptable adverse events (grade 3 or 4 serious adverse event, related to study drug)	X	X	X
	All other patients	X	X	X

* Can be documented clinically or radiologically.
** Follow for AEs until all other follow-up requirements are met. Follow patients for any ongoing or new grade 3 or higher toxicities thought to be related to protocol treatment until resolution.
***Follow patients for survival every 6 months; can be completed via telephone, in person, or review of medical records. Follow up is required from date of implementation (REB/IRB Approval at site) of this amendment. Deceased patients will require 1 follow up to document death.

5.5 **Criteria for Removal from Study**

Patients will be removed from study when any of the following criteria apply:

- Death
- Withdrawal of Consent,
- Lost to follow-up
- Termination by Regulatory Authorities
- Termination by the Principal Investigator

Should early termination of the study be necessary, active patients should be seen as soon as possible for End of Treatment (EoT) visit and the assessments for EoT should be performed as described in table for study follow-up visit. The Investigator will be responsible for informing the REB and/or other Regulatory Authorities of the early termination of the trial, as well as to ensure that adequate consideration is given to the protection of the patient's interests.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose Level	Cabozantinib/XL184
1	60 mg daily
-1	40 mg daily
-2	20 mg daily

XL184-Related Adverse Event Management

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities**.

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 6-1 and Table 6-2, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinurea, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate below. Guidance for the management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Cabozantinib Investigator's Brochure.

Treatment may be delayed and interrupted to allow for recovery of toxicity according to the guidelines below. Any other elective or planned interruptions to therapy must be discussed with the PI if the duration is greater than 2 weeks. Patients with cabozantinib-related toxicity at lowest dose level requiring further dosing modifications may continue on study, following dose interruption and sufficient recovery, if felt to be benefiting from treatment and upon discussion with PMHC PI.

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 5.0 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Interrupt cabozantinib treatment or reduce the cabozantinib dose. Add supportive care as indicated. • If cabozantinib dosing is interrupted, then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt cabozantinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction

CTCAE Version 5.0 Grade	Guidelines/Intervention
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.	

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 5.0 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until platelet count is ≥100,000/mm^3, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤1 and temperature to ≤38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery of ANC to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor and only with approval by the sponsor.

CTCAE Version 5.0 Grade	**Intervention**
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.
ANC, absolute neutrophil count; LLN, lower limit of normal Neutropenia: Grade 1 (LLN ≤ ANC < 1.5×10^9/L; Grade 2 (1×10^9/L ≤ ANC <1.5×10^9/L), Grade 3 (0.5×10^9/L ≤ ANC < 1×10^9/L), Grade 4 (ANC < 0.5×10^9/L). Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated). Thrombocytopenia: Grade 1 (Platelet count <LLN – 75×10^9/L); Grade 2 (Platelet count <75.0 – 50.0×10^9/L); Grade 3 (Platelet count ≤ 50 - 25×10^9/L); Grade 4 (Platelet count < 25×10^9/L).	

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson *et al.,* 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1 should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1 should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure). However given the potential of the 5-HT_3 antagonist ondansetron to prolong QTc, care should be taken to not exceed a daily dose of 16 mg. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing, and oral rinses (*e.g.*, with a weak solution of salt and baking

soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases. Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase elevation CTCAE v5.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib

≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval..

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × ULN, total bilirubin < 1.5 × ULN, aminotransferases ≤ baseline grade).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2 ×ULN), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase) or some other explanation of the injury (*e.g.*, viral hepatitis, alcohol hepatitis), as the combined finding (*i.e.*, Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.

Pancreatitis

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval..

Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures include the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (*e.g.*, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented in the table below.

In the case of study treatment-related skin changes (*e.g.*, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	If tolerable, continue cabozantinib at current dose. If intolerable, reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. If treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a treatment interruption is again required, the dose must be reduced when treatment resumes. Subjects should be

	instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, proceed to the management guidelines for Grade 3 PPE.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment.. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Subjects with known hypertension should be optimally managed prior to study entry. Patients are to be provided with a BP machine for at home daily monitoring for the first 28 days of treatment; further daily monitoring is to be determined at the physician's discretion. Decisions to decrease or hold the dose of study treatment should be based on BP readings taken by a medical professional and confirmed with a second measurement at least 5 minutes following the first measurement. However a physician can alter the patient's treatment if there is significant reasoning to due to their daily BP monitoring. Clinical judgment should be used in deciding

whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (see next Table below).

Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	**Treatment/cabozantinib Dose Modification**
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase anti-hypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of cabozantinib • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. • Increase anti-hypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
Hypertensive crisis or hypertensive encephalopathy	Discontinue all study treatment
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure	

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria	

Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in the next Table below.

Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1 mg/mg	• No change in treatment or monitoring
> 1 and < 3.5 mg/mg	• No change in study treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 hours on 24-hour urine collection. • Consider confirming with a 24-hour protein excretion within 7 days • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider holding cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose hold unless otherwise approved by PMHC PI. • Repeat UPCR within 7 days and once every week. If UPCR is < 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading). If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and

Urine Protein/Creatinine Ratio	Action To Be Taken
	monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue all study treatment

UPCR, urine protein/urine creatinine ratio

Guidelines for the Prevention of Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor lesions with cavitations or tumor lesions which invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity.
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases.
- Underlying medical conditions which affect normal hemostasis (*e.g.*, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel while on study treatment must be discontinued from cabozantinib treatment.

Developing cavitation of pulmonary tumors may be indicative of response. Patients deemed high risk of bleeding based on tumour location should be discontinued. If the investigator feels patient is low risk, a discussion should take place with PMHC investigator. Therapy may continue at the discretion of the PMHC PI.

Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula:
- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis .
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:
- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

Wound Healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing

has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half-lives) prior to elective surgery.

Endocrine Disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects (see Cabozantinib Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (*e.g.*, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

Guidelines for Prevention of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case by case basis.

Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org).
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status *e.g.*, severe or prolonged diarrhea.

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (*e.g.*, after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
XL184 (Cabozantinib s-malate, NSC 761968)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In

addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2438 patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 4, 2016[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypokalemia		
	Hypomagnesemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Musculoskeletal and connective tissue disorders - Other (muscle spasms)		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
Voice alteration			***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (hair color changes)		***Skin and subcutaneous tissue disorders - Other (hair color changes) (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib s-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib s-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Hypopituitarism; Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Anal fissure; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Hemorrhoids; Ileus; Pancreatitis; Rectal pain; Rectal ulcer
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (implant site inflammation); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatitis toxic); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Blood lactate dehydrogenase increased; Investigations - Other (D-dimer); Eosinophilia; Glucosuria; Investigations - Other (urine

ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (muscle hemorrhage);Osteonecrosis; Rhabdomyolysis; Myalgia; Neck pain; Osteoporosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (cerebral hematoma); Nervous system disorders - Other (hemiparesis); Spinal cord compression; Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Renal and urinary disorders - Other (azotemia); Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hypoxia; Laryngeal edema; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Oropharyngeal pain; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (splinter hemorrhages); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

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

7.2 Expedited Adverse Event Reporting

7.2.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP-Adverse Event Reporting System), accessed via the CTEP Web site (https://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (https://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.2.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. Each site will submit the electronic version of the CTEP-AERS report to the PMH Phase II Consortium Central Office. Once review by the lead group coordinator has taken place the report will be forwarded to NCI. CTEP-AERS provides a copy feature for other e-mail recipients.

7.2.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth

or progression: clinical deterioration associated with a disease process) should be submitted.

In order to ensure the timely fulfillment of both US and Canadian IND regulatory reporting requirements, all CTEP-AERS reports must be sent to the PMH Phase II Consortium Central Office within 3 working days from the date the event was known to the investigator.

- In the unlikely event that an adverse event occurs that does not meet the reporting requirements for CTEP-AERS, but does meet the definition of a Serious Adverse Event, a CTEP-AERS report must still be completed and sent to the Central Office within 3 working days of the event being known to the investigator. The event must be telephoned or e-mailed to Central Office within 1 working day.

- The PMH Phase II Consortium Central Office will be responsible for reporting to Canadian regulatory authorities all Serious Adverse Events that are both unexpected and related to study drug. The Central Office will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the Central Office by the NCI U.S.

- Investigators must notify their local Research Ethics Boards (REB/IRBs), according to their guidelines, of all SAE reports from their centre and file the report in their regulatory study binder. In addition, all reports sent out to centres by the PMH Phase II Consortium Central Office must be sent to local REB/IRBs, according to their guidelines. Documentation from the REB/IRB of receipt of these reportable events must be kept on file in each institution's regulatory binder.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.4 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms

7.5 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent: Cabozantinib (XL 184)

8.1.1 Cabozantinib (XL184) (NSC 761968)

Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Other Names: Cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: C28H24FN3O5.C4H6O5 **M.W.:** 635.6

Mode of Action: XL184 inhibits multiple RTKs implicated in tumor growth (progression of tumors in bone), metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

How Supplied: XL184 is supplied by Exelixis and distributed by the DCTD. XL184 is available in 20 mg and 60 mg tablets. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape. Each bottle contains 30 tablets.

XL184 Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

Storage: Store intact bottles at controlled room temperature, 20^0 to 25^0C.

Stability: "Stability testing of the intact bottles is on-going. XL184 is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container."

Route of Administration: Oral.

Method of Administration: Take XL184 on an empty stomach, 2 hours before and 1 hour after food. Do not crush or chew.

Potential Drug Interactions: XL184 is a substrate of CYP3A4. Coadministration of XL184 with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Examples of strong CYP3A4 inducers are rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, Phenobarbital, and St. John's Wort. Strong CYP3A4 inhibitors are ketoconazole, itraconazole, clarithroumycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications. Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

In vitro data, XL184 is not a P-gp substrate but may inhibit the P-gp transport activity.

XL184 is highly protein bound, 99.9%. Use caution when coadminister XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Cimetidine is a moderate CYP3A4 inhibitor. Avoid using cimetidine with XL184. Co-administration of gastric pH modifying drugs such as PPI, H2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is now allowed.

Patient Care Implications: Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Cimetidine or omeprazole is also available over-the-counter (OTC). Do not use cimetidine.

Availability
XL184 (cabozantinib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

XL184 (cabozantinib) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account

status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575. Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. ANCILLARY & EXPLORATORY ANALYSES

Rationale for HGF/MET pathway biomarkers

Oncogenic MET signaling is a consequence of various molecular mechanisms including gene amplification, mutation, over-expression, and autocrine activation, with the hierarchal relevance dictated by the tumour context. In addition, downstream HGF-MET signaling is complex and involves several networks that are already aberrantly regulated in human cancers including (but not limited to) PI3K/Akt and RAS-RAF-MEK-ERK. Therefore, molecular markers indicative of (1) the type of pathway aberration, (2) the mutational context of a patient's tumour or (3) the activation status of downstream signaling mediators, may indicate dependence on MET pathway, potentially acting as biomarkers of response to cabozantinib/XL-184.

Overview of correlative studies

Exploratory studies in archival tumour or fresh biopsies (if possible) will evaluate baseline mutational profiles and met amplification status as predictive markers of cabozantinib response.

Correlative studies evaluating tumour biology relevant to endometrial cancer will focus on (1) evaluating baseline status of MET (using standard FISH to identify MET amplification and sequencing to highlight activating mutations) and (2) tumour mutational profiling using a custom panel to assess a large panel of cancer-associated mutations.

All Correlative Studies will be conducted in the Applied Molecular Profiling Laboratory at Princess Margaret Cancer Centre following developed SOPs for both sample acquisition and performing individual assays.

9.1 Baseline Mutational Profiling of Archival Samples

All enrolled patients should have archival samples available for baseline mutational profiling. If archival tissue is not available, a sufficient tumour biopsy can be performed a minimum of 28 days prior to start of treatment if clinically reasonable to do so.

9.1.1 Collection of Specimen(s)

Paraffin embedded archival blocks are preferred, however if blocks cannot be released 15-20 unstained slides 4-5 microns each mounted on positively charged slides are also acceptable.

Mutational profiling and c-met amplification will be performed in the archival specimens of all patients.

9.1.2 Handling of Specimens(s)

Refer to Laboratory Manual.

9.1.3 Shipping of Specimen(s)

All archival specimens along with copies of the de-identified Pathology Reports should be sent to:

Correlative Studies Program
Princess Margaret Cancer Centre
610 University Avenue 7-420
Toronto, Ontario M5G 2M9
Tel: (416) 946-4501 ext 5047
Fax: (416) 946-4431
Email: CCRUcorrelativestudies@uhn.ca

9.2 **Peripheral Blood Collection**

Peripheral whole blood for SNP samples will be drawn at baseline for PK analysis. Samples will be obtained by standard venipuncture using plasma EDTA (lavender) tubes and processed following institutional SOPs.

9.2.1 Handling of Specimens(s)

Refer to Laboratory Manual.

Shipping of Specimen(s)

Refer to 9.1.3.

10. STUDY CALENDAR

Baseline (pre-study) evaluations are to be conducted ≤ 7 days prior to start of protocol therapy, unless specified differently in the study calendar. Scans and x-rays must be done ≤28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated. A cycle is 28 days long. A 14-day delay/lapse in treatment will result in the patient being removed from study unless specified differently; refer to section 6. Refer to the calendar for cycle 1 day 1 timelines. For subsequent cycles (2+), day 1 and day 15 assessments can be completed up to 3 days prior to day 1 or day 15 as applicable.

	Pre-Study	C1		C2-3		C4+	End of Treatment(30-37days after last dose) + Follow-Up[10]	Survival Follow-Up (every 6 months)
		D1	D15	D1	D15	D1		
Cabozantinib [5]		X----------X						
Informed consent [6]	X							
Demographics	X							
Medical History	X							
Physical examination	X	X[7]		X		X	X	
Height	X							
Weight	X	X[7]		X		X	X	
Vital signs (BP, pulse, RR, temp) [9]	X	X[7]	X	X	X	X	X	
ECOG performance status	X	X[7]	X	X	X	X	X	
Clinical laboratory tests [1]	X	X[7]	X	X	X	X	X[2]	
Urinalysis and UPCR	X	X[7]	X	X	X	X	X[2]	
PT or INR, and PTT	X	X[7]		X		X		
TFTs (TSH, free T3, free T4)	X	X[7]						
12-lead ECG	X	X[7]		X		X	X[2]	
Pregnancy test (β-HCG)[11]	X	X[7]		X		X		
Radiological Evaluation[3]	X	Radiologic measurements are to be performed at the end of cycle 3 and subsequently every 8 weeks regardless of any missed doses or holds..[3]					Must be provided for patients removed from study due to PD	
Tumor assessment [4]	X	Tumor measurements are to be completed at the end of cycle 3 and subsequently repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.						
Archival / Biopsy Tumor Tissue	X							
Correlative Blood	X							
Concurrent medications	X[8]	X----------X						
Adverse event evaluation		X----------X						
Survival Status								X

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; UPCR, urine protein/urine creatinine ratio

[1] Laboratory tests should include a standard hematology panel (CBC, differential, platelets) and chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein)
[2] For "Off Study" only, not Follow-Up
[3] For patients who have been on study for two years or longer, re-staging scans to be moved to every 12 weeks, irrespective of any missed doses or holds.
[4] All sites of known disease must be assessed, includes radionuclide bone scans in patients with known bony disease
[5] Dose as assigned; oral administration, continuous for 28 days, at the same time once every day, on an empty stomach, do not eat 2 hours before and 1 hour after taking Cabozantinib
[6] Completed prior to study related tests
[7] If completed within 4 days prior to day 1 it does not need to be completed
[8] Concurrent medications recorded as of 15 days pre-registration.
[9] Blood pressure to be measured by the patient on a daily basis for the first 28days (recorded on the diary card appendix E); it is the physician's discretion if further monitoring is required. Refer to section 6 when determining dose modifications due to blood pressure changes.
[10] Refer to 5.4 for subsequent follow-up expectations
[11] For Women of child bearing potential

11.1 **Antitumor Effect – Solid Tumors**

For the purposes of this study, patients should be evaluated by cross-sectional imaging at baseline, at the end of cycle 3 and then every 8 weeks irrespective of missed or held doses. (every 3 cycles (12 weeks) for patients on study for 2 years or longer)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with XL184.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study, including baseline. Patients will not go from PR to SD.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. 12-week PFS is defined as the percentage of patients progression free 12 weeks from starting treatment.

11.1.7 Overall Survival

OS is defined as the duration of time from start of treatment to time of death.

11.1.8 Response Review

During trial tumour measurements will be assessed by a study radiologist. On study completion all responses will be assessed by an independent expert to confirm response.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for entering their data into the Medidata Rave system and submitting copies of their source notes to the Central Office / Coordinating Centre within 3 weeks of the end of cycle. Please refer to Appendix G, Data Management Guidelines, for further details regarding data submission requirements.

The Central Office / Coordinating Centre is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 **Collaborative Agreements Language**

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of

human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Evaluation of the experimental cohorts of this trial is based on a modified Simon two-stage design with co-primary endpoints of response rate (RR) and 12-week progression-free survival (PFS). A maximum of 36 evaluable patients will be enrolled to each histological cohort to discriminate between tumor RR rates of 30% vs. 10% and 12-week PFS rates of 55% vs. 30% (corresponding to median PFS of 3.4 to 1.7 months). Each cohort will be reviewed on its individual results. If at least 8 responses (at least 22%), or at least 16 instances of 12-week PFS (at least 44%), were observed among the 36 evaluable patients, this regimen would be considered worthy of further testing in that particular histological subgroup of endometrial cancer.

Stage I has a planned accrual of 18 patients per histological cohort. If no more than 2 objective responses (no more than 11%), and no more than 6 instances of 12-week PFS (no more than 33%) were observed amongst the initial 18 patients accrued per histological cohort, study would

be terminated early and declared negative. Study will go to stage II if at least 3 objective responses or at least 7 instances of 12-week PFS are observed in stage I in either cohort. Each cohort will be reviewed on its individual results. If one cohort is negative the other cohort may still proceed to stage II.

The design yields at least 86% power to detect a true objective response rate of at least 30%. It yields at least 90% power to detect a true 12-week PFS rate of at least 55% (median PFS of 3.4 months). It yields at least 0.94 probability of a negative result if the true objective response rate is no more than 10% and the true 12-week PFS rate is no more than 30% (median PFS of 1.7 months), with approximately 0.53 probability, at least, of early negative stopping in this case. These last two probabilities are calculated assuming that tumor response rate and PFS rate are uncorrelated. If they are positively correlated, as is likely, the probabilities will be a bit higher.

Patients with rare histology endometrial cancer (including clear cell, carcinosarcoma) will be enrolled in an exploratory cohort in which > 4/10 objective responses in a particular histology would suggest significant activity. A maximum of 30 patients will be accrued to this exploratory cohort.

Adverse events will be graded using CTCAE v 5.0.

13.2 Sample Size/Accrual Rate

In the experimental cohort, stage I has a planned accrual of 18 patients per histological cohort. If > 2 PRs or > 6 instances of 12-week PFS, accrual will proceed to Stage II with a planned total accrual of 36 evaluable patients per histological cohort. Accrual to the exploratory cohort will proceed as long as patients are being accrued to experimental cohort to a maximum of 30 patients.

Estimated accrual is 2-3 pts per month and is expected to take 24 to 36 months.

13.3 Analysis of Secondary Endpoints

Secondary endpoints to be evaluated include:

- baseline molecular status of archival tumour (c-met amplification & mutation status)
- pharmacodynamic responses in levels of soluble, circulating angiogenic factors
- overall survival

Correlating with clinical response

13.4 Reporting and Exclusions

13.4.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with XL184.

13.4.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-7 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-7 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
- Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

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

The patient _____ is enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib)**. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

XL184 interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

XL184 interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is **CYP3A4**. This enzyme breaks down XL184, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. XL184 must be used very carefully with these medicines, or you may need to switch to alternate medications.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors of **CYP3A4**."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/ or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age.

Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.

- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking XL184 (cabozantinib).

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib).** This clinical trial is sponsored by the NCI. **XL184 (cabozantinib)** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**XL184 (cabozantinib)** interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers or inhibitors of **CYP3A4.**" ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/ for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX D DATA MANAGEMENT GUIDELINES

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the PMH Phase 2 Consortium Central Office. The site will be required to complete a paper Eligibility Checklist case report form (CRF) at the time of patient registration. All other data will be collected on electronic case report forms (eCRFs) in the Medidata Rave system. Site staff access to Medidata Rave will be initiated at the time of site activation. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline eCRFs	Within 3 weeks of on study date
On Treatment (Cycle) eCRFs	Within 3 weeks of the end of each cycle of treatment
Off Treatment eCRFs	Within 3 weeks of the patient coming off-study
Short Follow-up eCRFs	Within 3 weeks of the patient coming to clinic.
Final eCRFs	Within 3 weeks from the follow-up period being complete or of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to CTEP-AERS guidelines

Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs will be completed according to the schedule noted above and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted to the PMHC Phase 2 Consortium Central Office for review. All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number.

eCRF completion guidelines are available for all sites.

Monitoring

Central data monitoring will take place throughout the trial at the Central Office. On-site monitoring will be performed once a year at participating sites during which a subset of PMHC studies will be picked for on-site monitoring.

Data in the Medidata Rave eCRFs will be monitored on a regular basis and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site prior to the quarterly submission of data to CDUS.

Patient Registration

- Refer to section 4 of the protocol

Data Safety

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent.

Regulatory Requirements

- Please submit all required documents to the PMH Phase 2 Consortium Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- All investigators must have a current NCI investigator number on file with the PMH Phase 2 Consortium Central Office.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the PMH Phase 2 Consortium Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergoes such training.
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- OPRR assurance numbers for each institution are required
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the PMH Phase 2 Consortium Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the PMH Phase 2 Consortium Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to PMHC
- Continuing approval will be obtained at least yearly until follow-up on patients is completed

CTEP-assigned Protocol # 9322
Local Protocol # PHL-086

APPENDIX E PATIENT'S STUDY DRUG DIARY
XL184 (Cabozantinib)

Today's Date _____ Patient Initials _____ Patient Study ID _____

INSTRUCTIONS
1. Complete one form for each cycle of treatment.
2. You will take **____ 20 mg and ___ 60 mg** XL184 tablet(s) each day (____ mg total dose), once a day, continuously over a 28 day period. You must fast 2 hours before and 1 hour following each dose of XL184.
3. Swallow each tablet whole. Do not crush or chew the tablets.
4. Record the date and time you took the tablet.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottle of XL184 at the end of each cycle.
7. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Time of Dose	XL184 Dose (mg)	Blood Pressure	Comments
1				/	
2				/	
3				/	
4				/	
5				/	
6				/	
7				/	
8				/	
9				/	
10				/	
11				/	
12				/	
13				/	
14				/	
15				/	
16				/	
17				/	
18				/	
19				/	
20				/	
21				/	
22				/	
23				/	
24				/	
25				/	
26				/	
27				/	
28				/	

Physician's Office will complete this section:
1. Start date for this cycle _____ End date for this cycle _____
2. Date patient was removed from study_____
3. Total number of tablets taken this cycle _____

The above information has been reviewed with the patient: Physician/Nurse Signature/Date _____