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Reason for amendment: Change to CIMAC studies

#	Section	Comments
1.	2.4.4.1 and 9.8.4.1	Changed mention of specific CIMACs working with Adaptive/on TCRseq to simply “CIMACs”, as multiple CIMACs are working on TCRseq in this trial.
2.	9.4.3	Updated EET Biobank’s address
3.		
4.		

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TITLE: A Randomized Phase 2 Study of Cabozantinib in Combination with Nivolumab in Advanced, Recurrent Metastatic Endometrial Cancer.

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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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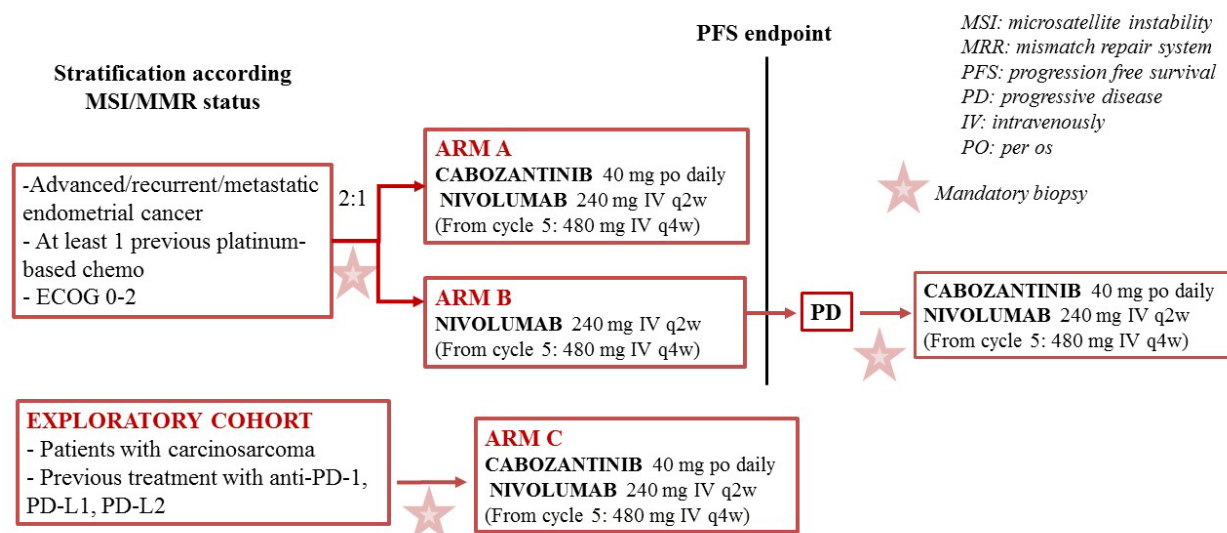
NCI-Supplied Agents: Nivolumab (BMS-936558, MDX-1106, ONO-4538) (NSC #748726); XL184 (cabozantinib) (NSC #761968)

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SCHEMA



Cycle of 28 days (4 weeks) and evaluation of response every 8 weeks

Safety assessment after first 6 [in arm A + carcinosarcoma (arm C)] → if ≥ 2 DLT a dose de-escalation will be applied (Cabozantinib 20 mg/day)

STUDY SUMMARY

This is an open label randomized phase II study assessing the activity of the multi-targeted tyrosine kinase inhibitor XL184 (cabozantinib) in combination with the immune checkpoint inhibitor nivolumab (arm A) versus nivolumab alone (arm B) in patients with advanced, recurrent or metastatic endometrial cancer. Patients will be randomized in a 2:1 ratio and stratified according to microsatellite (MS) status assessed with genomic analysis or mismatch repair system (MMR) status defined in immunohistochemistry (MS stable or MMR intact versus MS instable or MMR abnormal). MS or MMR status will be defined on archival tissue as per local guidelines. Subsequently, MMR status in the Pathology Department at Princess Margaret Cancer Centre for exploratory purposes. Both tests will be performed on archival tissue and on baseline biopsy and correlated with patient outcome.

A total of 54 patients will be enrolled, 36 in arm A and 18 in arm B.

The primary end-point is progression free survival (PFS). Secondary end-points are: overall response rate (ORR), overall survival (OS), safety and correlation between PD-L1, CD3, CD4, CD8 expression in tumor and patients' outcome. Correlatives studies will assess PD-L1 expression, TILs infiltrates (CD3, CD4 and CD8), MS and MMR status, MET amplification, genomic profiling and immune microenvironment in archival tissue and baseline biopsy and their correlation with patient outcome. Changes in immune markers in peripheral blood will be also assessed at baseline and during treatment.

Eligible patients include those with diagnosis of advanced/recurrent/metastatic epithelial endometrial cancer regardless of histological subtype, and with radiological progression after at least one line of previous platinum-based chemotherapy. Patients with diagnosis of endometrial carcinosarcoma will be enrolled in the exploratory cohort (arm C) receiving combination of cabozantinib and nivolumab and will not be part of the statistical analysis. A mandatory baseline biopsy will be required for correlative analysis, and performed ≤ 28 days and ≥ 7 days before starting treatment. One formalin-fixed paraffin-embedded (FFPE) slide obtained from baseline line biopsy will be used for pathology review performed at Princess Margaret Cancer Centre.

In arm A, patients will receive cabozantinib at 40 mg/day orally continuously (day 1-28) and nivolumab at flat dose of 240 mg IV every 2 weeks (day 1 and 15) in cycles of 28 days. In arm B patients will receive nivolumab at 240 mg IV every 2 weeks (day 1 and 15) with a cycle lasting 28 days. After the first 4 cycles, nivolumab will be administered at the dose of 480 mg IV every 4 weeks in both arms, if deemed tolerable to the patient by the treating physician. Response will be assessed every 8 weeks (+/- 7 days), according to RECIST 1.1 criteria. Adverse events will be graded using CTCAE v5.0.

Patients enrolled in arm B (nivolumab alone) will, at investigator and patient discretion, have the option to be crossed over to cabozantinib and nivolumab combination at the time of progression provided they meet the cross-over eligibility detailed in [section 3.3](#). A mandatory biopsy at the time of progression will be required to analyze changes in molecular and immunological landscape after check-point inhibitor treatment. These patients will be analyzed as part of the exploratory cohort (arm C) from the time of cross-over.

Patients previously treated with anti-PD-, anti-PD-L1 or anti-PD-L2 (not necessary as last line of treatment) can be enrolled in the exploratory cohort (arm C) at the time of progression from last line of treatment and will not be part of the statistical analysis. A baseline biopsy will be requested before enrollment.

A safety assessment will be performed after the 6 patients are randomized to the combination arm have each completed one cycle of treatment (patients from arm A and patients with carcinosarcoma in arm C). Details can be found in section 5.3.

Sample size estimation: a one-sided log-rank test with an overall sample size of 54 subjects (36 in arm A and 18 in arm B) achieves 80% power at a 0.10 significance level to detect a hazard ratio of 0.50 when the control group median survival time is 3 months. The study lasts for 24 months, of which subject accrual (entry) occurs in the first 18 months. 5% loss of follow-up is considered for this sample size estimation.

Dose De-Escalation Schedule		
Dose Level	Dose	
	<i>XL184(Cabozantinib)</i>	<i>Nivolumab</i>
Level 1	40 mg po daily	240 mg IV Q2W 480 mg IV Q4W from cycle 5
Level -1	20 mg po daily	240 mg IV Q2W 480 mg IV Q4W from cycle 5

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1. OBJECTIVES

1.1 Primary Objectives

- To evaluate the clinical anti-tumor activity of XL184 (cabozantinib) and nivolumab based on progression free survival (PFS) in patients with advanced, recurrent or metastatic endometrial cancer previously treated with at least one line of platinum-based chemotherapy compared to patients receiving nivolumab alone.

1.2 Secondary Objectives

- To evaluate the efficacy of XL184 and nivolumab in terms of overall response rate (ORR) compared to nivolumab alone.
- To evaluate overall survival (OS) of patients receiving XL184 and nivolumab compared to patients receiving nivolumab alone.
- To evaluate the safety of combination treatment using XL184 and nivolumab in patients with advanced, recurrent metastatic endometrial cancer.
- To evaluate correlation between PD-L1 expression, CD3, CD4 and CD8 infiltrates and outcome (PFS, ORR, OS).
- To compare PD-L1 expression, CD3, CD4 and CD8 infiltrates in the primary tumor (archival tissue) and in the tissue from baseline biopsy.
- To assess activity (PFS, ORR and OS) of nivolumab alone or in combination with XL184 according to MSI/MMR status.

1.3 Exploratory Objectives

- To assess activity (PFS, ORR and OS) of XL184 and nivolumab in patients progressed after previous exposure to anti PD-1, PD-L1 or PD-L2 agents or crossed-over from single agent nivolumab, and in patients with diagnosis of carcinosarcoma.
- To compare MSI and MMR status, in the primary tumor (archival tissue) and in the tissue from baseline biopsy.
- To assess the genomic and immune-markers landscape at baseline on tumor tissue and changes in immune landscape in peripheral blood during treatment and correlate with outcome

2. BACKGROUND

2.1 Endometrial Cancer

Of all gynecologic malignancies, endometrial cancer (EC) has the highest incidence, with an estimated 61,380 new cases diagnosed in the United States in 2017, and 10,920 women who will succumb to their disease¹. Despite these statistics, the majority of women are diagnosed with early stage endometrial cancer, with only ~8% of patients are diagnosed with stage IV disease. Although that percentage is small, up to 25% of those patients experience recurrence after surgery.

Type I or estrogen-dependent endometrioid EC represents 70-80% of cases and is usually secondary to estrogenic stimulation and characterized by low grade, endometrioid differentiation, hormone-receptor positivity. The most common genomic mutations found in Type I EC are PTEN, PI3K/AKT pathway, KRAS, CTNNB1, ARID1A, and FGFR2. Microsatellite instability (MSI) has frequently been reported. Type 2 EC consists of estrogen-independent non-endometrioid carcinoma such as serous, clear cell and mixed adenocarcinoma². The most common mutations are TP53, PI3KCA and PPP2R1A, and there is a 25% incidence of ERBB2 amplification but microsatellite instability is rare. TP53 has also been detected in high grade endometrioid endometrial cancer and in carcinosarcoma².

The Cancer Genome Atlas (TCGA) has sequenced the exomes of 248 endometrial cancers and, based on the presence of somatic nucleotide substitutions, copy number variations, and MSI, has created a new, four-group classification: 1) ultra-mutated group with a high rate of mutations, also called Polymerase Epsilon (POLE) group, based on the 100% frequency of mutation in this polymerase involved in DNA replication; 2) hyper-mutated group characterized by MSI; 3) group with lower mutation frequency and includes most of the endometrioid cancers with microsatellite stable (MSS); and 4) serous-like cancer with a low mutation rate but high copy number alterations³. Interestingly, the ultra-mutated-POLE and the hyper-mutated groups have a higher level of neo-antigens and tumor-infiltrating-lymphocytes (TILs) leading to an increase in immune system activation compared to other subtypes of endometrial cancer. TILs of POLE and MSI endometrial cancer subtypes have higher expression of PD-1 and PD-L1⁴ and have been described as a molecular subtype with longer progression-free survival by TCGA³. MSI is observed in ~ 20-40% of endometrioid EC but is uncommon in serous subtype³.

Type I cancers could benefit from hormonal manipulation and are usually known to be resistant to standard chemotherapy, while Type II endometrial cancers are more aggressive, usually of high-grade serous histology, and typically present with advanced stage disease⁵. Presently, advanced or relapsed endometrial cancer has a poor prognosis with few effective agents available. Standard first-line chemotherapy is a combination of carboplatin and paclitaxel with a response rate (RR) of 40-50%⁶. Second-line chemotherapies usually have a low RR (<15%) with progression free survival (PFS) of ~3 to 4 months⁷.

As such, there is a significant unmet medical need for this patient population. This study is looking to advance novel agents that will improve outcomes, and identify predictive biomarkers to better select patients most likely to benefit from specific treatments.

2.2 CTEP IND Agents

2.2.1 XL184 (cabozantinib)

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis⁸. 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. In vivo pharmacodynamic activity of XL184 against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

RTKs regulate many processes, including: cell growth and survival, organ morphogenesis, neovascularization, and tissue repair⁹. Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand, have 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 vivo⁸. 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) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of c-Met by mutation or gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorigenicity 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) the 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 vivo⁹.

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity¹⁰, either by means of c-Met kinase overexpression¹¹, activating c-Met gene mutations and/or amplification¹¹⁻¹³, or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF^{11,14,15}. These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis¹⁴.

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability¹⁶. Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium of most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer¹⁷. 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 the 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 tumors¹⁸. 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 metastases¹⁹. 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 days²⁰. 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/kg²¹. 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 pre-dose 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 bone²². 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 treatment⁸. 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 trials²³. 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, specifically. 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/kg²³. 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-Met²¹. 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 μ M were associated with efficacy²³. In rats, plasma concentrations in the range of 5 to 15 μ M were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 μ M were observed at highly efficacious doses in mice. These results were consistent with in vivo target modulation studies in mice which demonstrated long (4-10 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 rats²³. 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 [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single XL184 oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg)²³. With repeat daily oral dosing in rats, systemic exposure (AUC_{0-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 C_{max} and AUC_{0-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 (C_{max} and AUC_{0-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 absorption⁸. With repeat daily dosing, exposure (C_{max} 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 tissues⁸. 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 study²³. 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 doses 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 (2017). Safety and efficacy information, from the 2017 Investigator's Brochure, is summarized below.

Phase 1 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 (using capsules [25 and/or 100mg] for two, 14-day cycles) were enrolled. The capsule MTD was determined to be 175 mg qd²⁴. Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease enrolled in the dose expansion phase, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of $\geq 30\%$, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

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 XL184 in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg XL184, dosed as one 100 mg capsule and three 25 mg capsules 30 minutes after administration of a high fat breakfast) or Reference (175 mg XL184, 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 XL184 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 XL184 tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg XL184, dosed as one 100 mg tablet) or Reference (100 mg XL184, 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 XL184 PK.

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 XL184 on the CYP isozyme CYP2C8. The effect of daily dosing of 175 mg XL184 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 XL184 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.

Phase 2 Studies

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.

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)⁸. 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, 2017).

Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial XL184-001 showed dose proportional increases in maximum plasma concentration (C_{max}) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg)²⁴. Terminal-phase half-life (t_{1/2,z}) values were 59.1 to 136 hours⁸. After repeat dosing, t_{1/2,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 15²⁴. 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 t_{1/2, z} of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximate mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for C_{max} and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 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 [AUC_{0-last} or AUC_{0-inf}]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean AUC_{0-last} and AUC_{0-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 t_{1/2, z} of cabozantinib [mean t_{1/2, z}: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max} to 6 hours from 4 hours (fasted). The highfat meal also significantly increased both the cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of AUC_{0-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 hours before and 1 hour after each cabozantinib dose).

2.2.2 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor²⁵. PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of

nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients²⁶.

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses, or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA)²⁵. PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells, dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment²⁷. Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors and is associated with poor prognoses based on OS in many tumors including: melanoma²⁸, renal²⁹⁻³¹, esophageal³², gastric³³, ovarian³⁴, pancreatic³⁵, lung³⁶, and other cancers²⁵.

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8⁺ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2016). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a K_d = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications²⁵. In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity (AUC_{0-∞}), with low to moderate inter-subject variability observed at each dose level²⁵. Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses³⁷. Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively³⁸. In the RCC

cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥ 1 year³⁹.

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen)²⁶. The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet⁴⁰. No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined⁴¹. Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group²⁶, grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these events.

Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of immunohistochemistry (IHC) staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count²⁶. With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon- γ (IFN- γ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

2.3 Rationale

Angiogenesis pathway in endometrial cancer

The angiogenesis pathway plays a relevant role in the development and progression of endometrial cancer. Antiangiogenic agents have shown some activity in endometrial cancers with 6 months progression-free survival (PFS) reaching 30-40%. Despite this, response rates remain low (Table 2-1).

Table 2-1 Selected phase 2 trials of antiangiogenic agents in recurrent endometrial cancer

Agents	References	6 Month PFS (%)	RR (%)
Thalidomide	McMeekin et al ⁴²	8	13.5
Bevacizumab	Aghajanian et al ⁴³	40	13.5
Aflibercept	Coleman et al ⁴⁴	41	7
Sorafenib	Nimeiri et al ⁴⁵	29	5
Sunitinib	Castonguay et al ⁴⁶	30.3	18.1
Brivanib	Powell et al ⁴⁷	30.2	18.6
Nintedanib	Dizon et al ⁴⁸	21.9	9.4
Trebananib	Moore et al ⁴⁹	15.6	3.1
Cediranib	Bender et al. ⁵⁰	29	12.5

Antiangiogenic activity is reduced due to up regulation of other pathways, and MET signaling has been identified as one of the possible mechanisms of resistance to antiangiogenic treatment⁵¹. Hyperactivation of the HGF (hepatocyte growth factor)/MET pathway is present in 60% of endometrial cancer and is relevant in endometrioid and serous histology⁵². Targeting this tyrosine kinase receptor inhibits angiogenic and mitotic pathways¹⁴. Cabozantinib is a multi-target tyrosine kinase inhibitor (TKI) with its primary targets as both c-MET and VEGFR2, and additional targets including RET, AXL, KIT and TIE-2²¹. Cabozantinib has been approved for the treatment of renal cell and medullar thyroid cancers^{53,54}. Preliminary data on its efficacy in endometrial cancer was presented at the 2017 American Society for Clinical Oncology (ASCO) conference (NCT01935934)⁵⁵. In this study, patients with metastatic endometrial cancer who had progressed after first line chemotherapy or had relapsed within 12 months from the end of adjuvant chemotherapy received 60 mg cabozantinib daily continuously. A total of 102 patients have been enrolled. Patients with non endometrioid/non serous subtype were enrolled in an exploratory cohort (31 subjects) and were not part of the statistical analysis. Preliminary efficacy data was analyzed on 33 patients with endometrioid subtype and 34 with serous subtype. In the endometrioid subtype, RR was 18% and median PFS 4.8 months; in the serous subtype, RR was 12% and median PFS 4.0 months. The treatment was well tolerated and the most frequent toxicities (on 101 evaluable patients) included: fatigue, nausea, diarrhea, and palmar-plantar erythrodysesthesia. The most frequent G3/4 adverse event was hypertension. Fistula or perforation occurred in 4/71 patients in the experimental cohort and in 4/31 in the exploratory cohort. Interestingly, sign of activity of cabozantinib has been observed in patients with endometrial carcinosarcoma. Nineteen women with relapsed/progressive carcinosarcoma have been enrolled and 1 partial response and 8 stable disease at 12 weeks observed⁸². This preliminary sign of activity warrants further investigation, in this rare and aggressive histological subtype, given the lack of effective treatment.

Cancer cells commonly become resistant to TKIs, thus a strategy to overcome resistance may be a combination approach with agents that have synergistic effects. Different studies have suggested that chemotherapy, radiation therapy, or targeted small molecule inhibitors can alter the antigenic expression

of cancer cells. This results in increased susceptibility of cancer cells to T cell-mediated lysis or the alteration of the immune landscape peripherally or in the tumor microenvironment⁵⁶. Vascular endothelial growth factor (VEGF) has shown the ability to affect the functional maturation of dendritic cells, which are the most effective antigens presenting cells (APCs) in the induction of primary immune responses. Targeting VEGF not only causes angiogenesis inhibition but also increases the immune response against cancer cells⁵⁷. In murine tumor cells, cabozantinib has shown to be able to increase the effector cells and reduce the negative immune regulatory cells [T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs)] and this effect is increased when a cancer vaccine against a self-antigen is added to cabozantinib⁵⁸. A study presented at ASCO 2014 of urothelial carcinoma patients treated with cabozantinib demonstrated that patients with low Tregs at baseline have an improvement of partial response (PR), PFS, and overall survival (OS), as well as decreases in Tregs. Overall, from peripheral blood samples obtained from patients with advanced/refractory metastatic urothelial carcinoma undergoing treatment with cabozantinib, PD-1 expression in Tregs increased after treatment. However, patients with a PD-1 change below the median showed a strong trend to improved PFS compared to those with increased PD-1 above the median ($p=0.035$)⁵⁹. Additionally, it has been demonstrated that cMET pathway activation regulates the expression of the negative co-stimulatory protein PD-L1 on renal cancer cells and this inhibits immune mediated cancer cell killing⁶⁰. A study of patients with triple negative breast cancer treated with cabozantinib has analyzed circulating cells as biomarkers and provided evidence to show that cabozantinib induces activation of the immune system in this subset of patients⁶¹. Tyrosine kinase inhibitors not only alter the tumor microenvironment but also immune cell infiltration in the tumor. Therefore, combining them with immunotherapy agents may increase their activity.

Checkpoint Inhibitors in endometrial cancer

Different immunotherapies have been evaluated in gynecologic cancer, and immune checkpoint inhibitors are the most promising agents currently in development. Interestingly, expression of PD-1 and PD-L1 is higher in endometrial cancer than in other gynecological cancers^{62,63}. Preliminary data have also shown that immune checkpoint inhibitors may have higher activity in patients with MMR (mismatch repair)-deficient endometrial cancer⁶⁴. Tumors with microsatellite instability (MSI) or polymerase epsilon (POLE) mutation have high neo-antigen loads and an increased number of CD4+ and CD8+ tumor infiltrating lymphocytes but also increased expression of PD-1 and PD-L1⁴. MSI is observed in ~ 20-40% of endometrioid EC and is rare in other³. Pembrolizumab (anti PD-1 agent) has demonstrated preliminary antitumor activity in patients with advanced endometrial cancer. In 24 patients with PD-L1 positive (> 1% in tumor cells, immune-infiltrates, stroma and assessed by Qualtek IHC) EC treated with Pembrolizumab in the phase Ib Keynote-028 (NCT02054806) trial, 13% (n=3) of patients achieved partial response and 13% (n=3) had stable disease⁶⁵. Nineteen patients were evaluable for MSI status and 1 had MSI-high status and 18 non-MSI-high. Among the 3 patients that achieved a partial response, 1 was found to have POLE mutation, one MSS tumor and one MS status unknown. Treatment related adverse events have been reported in 13 patients (54.2%) and the most common were fatigue, pruritus, pyrexia and decrease appetite. In a single institution phase 2 study, a 70% RR was observed within MSI endometrial cancer patients (2 CR and 4 PR on a total of 9 patients)⁶⁶.

Nivolumab is a fully human IgG4 monoclonal inhibitory antibody against the programmed cell death 1 (PD-1) receptor that has been approved for the treatment of advanced melanoma, non-small cell lung carcinoma, renal cell carcinoma and classical Hodgkin's lymphoma. Several studies have confirmed the efficacy and safety of nivolumab in solid tumors⁶⁷⁻⁷⁰.

Combination of TKI and Checkpoint Inhibitors

In renal cell cancer, different combinations of anti PD-1/PD-L1 and anti-angiogenic agents are under investigation with preliminary data being reported ⁷¹⁻⁷⁵ and in these trials, the rate of response was significantly high in patients who had received previous lines of treatment; however, increased toxicity was also found (Table 2-2).

Table 2-2 Adverse events

Treatments	Adverse Events
Nivolumab + sunitinib or pazopanib⁷¹	82% G3-G4 AE 70% G3-G4 AE, Close for dose limiting liver toxicity
Atezolizumab + bevacizumab⁷²	33%
Pembolizumab + axitinib⁷³	1 patient with \geq G3 liver toxicity
Pembrolizumab + pazopanib⁷⁴	65% \geq G3 liver toxicity
Cabozantinib + nivolumab	G3-G4 AE: 23% hypertension, 17%neutropenia, 17% lipase increase, 13% hypophosphatemia
Cabozantinib+ nivolumab+ipilimumab⁷⁵	G3-G4: 19% hypophosphatemia, 19% hypertension, 13% fatigue, 13% Hyponatremia, 17% lipase increase

In endometrial cancer, cabozantinib has shown preliminary activity with no relevant difference between histological subtypes^{55,82}. Checkpoint inhibitors may have efficacy in endometrial cancer patients, mainly when a higher burden of mutations is present⁶⁴. The association of cabozantinib and immune checkpoint inhibitors might increase response rate and duration of response; however, higher incidences of side effects have been reported when combining antiangiogenic agents and checkpoint inhibitors⁷¹⁻⁷⁴. Among the different anti PD-1/PD-L1 agents, nivolumab has demonstrated a good tolerability and safety profile. Early results from phase I trial assessing combination of cabozantinib and nivolumab in patients with metastatic genitourinary tumors (NCT02496208) have shown that this combination is safe and active, with a significant increase in response rate with the combination⁷⁵. The recommended phase II dose has been 40 mg os daily for cabozantinib and 3 mg/kg every 2 weeks IV for nivolumab. A flat dose of nivolumab at 240 mg every 2 weeks has shown similar median exposure and benefit-risk profile.

Moreover, preliminary findings showed that cabozantinib modulates the immune microenvironment. Myeloid-derived suppressor cells (MDSCs), which accumulate as a result of tumor-induced alterations in myelopoiesis, impair T-cell effector functions directly, as well as indirectly, via the induction of regulatory T-cell formation⁷⁶. Given that MDSCs are known to inhibit T-cell sensitization to tumor antigens, their depletion may be clinically desirable in the context of immunotherapy treatment. VEGF has been implicated in the development and regulation of MDSCs, and for example, sunitinib has demonstrated an ability to reverse tumor-induced immunosuppression via reduction of MDSCs⁷⁷. This reduction was associated with an improvement of effector T-cell function, T-cell interferon-gamma production, and a decline in regulatory T-cell (Tregs) numbers.

Other VEGF inhibitors have shown the ability to augment the immune system by inducing autophagy and suppressing activation of tumor-associated macrophages, which correlates with tumor micro-vessel density and VEGF levels⁷⁸. Additionally, VEGF has shown the ability to dramatically affect the functional maturation of dendritic cells, which are the most effective antigen-presenting cells (APCs) in the induction of primary immune responses⁷⁷. Resulting cells have a low level of major histocompatibility complex class II expression and a reduced ability to take up soluble antigens⁵⁷. These

results highlight that VEGF inhibition may not only inhibit angiogenesis but may also improve the functional potency of antigen presentation and, consequently, assist in the development of immunity against cancer cells themselves.

Given the rationale and potential activity to combine cabozantinib with and PD-1/PD-L1 blockade in EC, we propose to assess the activity and safety of combining cabozantinib and nivolumab in the EC population. This will be a randomized Phase 2 trial comparing nivolumab alone versus the combination of nivolumab and cabozantinib. Given the prognostic significance of MSI status, patients will be stratified according to MSI status.

Check-point inhibitors have shown to be active in different cancer types. However, the majority of patients experience primary or acquired resistance. Different studies are ongoing to define potential mechanism of anti-PD-1/PD-L1 resistance. A study from Hugo et al. described that the concomitant expression of genes involved in mesenchymal transition, angiogenesis or other microenvironment processes could potential lead to check-point inhibitors resistance⁸³. Expression of angiogenesis-related genes could induce immunosuppression^{84,85} and they were found to be higher expressed in patient with resistance to anti-PD1/PD-L1 compared to the one responding to treatment⁸³. In consideration of the potential role of anti-angiogenic agents in restoring sensitivity to immune check-point inhibitor, we will explore efficacy of cabozantinib and nivolumab combination in patients with endometrial cancer who progressed after previous treatment with anti PD-1, PD-L1 or PD-L2 antibody. These patients will be enrolled in an exploratory cohort and will not be part of the statistical analysis for the primary objective, receiving the combination of cabozantinib and nivolumab.

2.4 Correlative Studies Background

2.4.1 Definition of MMR Status on Baseline Biopsy and Archival Tissue with IHC

According to The Cancer Genome Atlas (TCGA), endometrial cancers are classified based on the presence of somatic nucleotide substitutions, copy number variations, and MS status. Four groups can be identified: 1) ultra-mutated group with a high rate of mutations, also called Polymerase Epsilon (POLE) group based on the 100% frequency of mutation in this polymerase involved in DNA replication; 2) hyper-mutated group characterize by MSI; 3) group with lower mutation frequency and includes most of the endometrioid cancers with microsatellite stable (MSS); and 4) serous-like cancer with a low mutation rate but a high copy number alterations³.

MSI is a specific tumor phenotype characterized by a deficiency in the mismatch repair system (MMR). Repetitive nucleotide sequences are present in the genome, known as microsatellite regions. When DNA polymerase is deficient, these sequences are not adequately transcribed. MMR is able to detect and correct the transcriptional error. However, if the MMR system is deficient, errors in the microsatellite regions are not identified and repaired, causing genome instability. Deficiency in the MMR system may be due to germline or somatic mutations in one of the genes encoding for these proteins (most common: MLH1, MSH2, MSH6, PMS2) or due to gene promoter methylation⁷⁹.

MSI tumors are characterized by a high load of neo-antigens and significant immune cells infiltration. The neo-antigens load is 7-fold higher in MSI tumor compared to MSS that can justify the presence of

increased tumor infiltrated lymphocytes. Moreover, MSI and POLE endometrial carcinoma overexpress PD-1/PD-L1⁷⁹.

Preliminary data have shown increased activity of immune checkpoint inhibitors in tumors harboring a MMR deficiency⁶⁴. A phase II study reported a RR of 70% when patients with MMR-deficient endometrial cancer are treated with Pembrolizumab⁶⁶

MSI can be assessed through IHC with good accuracy, assessing 4 MMR proteins: MLH1, PMS2, MSH2 and MSH6².

Immunohistochemistry for MMR proteins has comparable performance characteristics to MSI testing and a high concordance rate⁸⁰. In contrast to MSI status assessment, immunohistochemistry offers the advantage of defining which MMR gene is mutated or methylated. MLH1 and MSH2 are stable without their dimer partners (PMS2 and MSH6, respectively), but not the opposite. As a result, tumors with an MLH1 mutation will show loss of both MLH1 and PMS2 on immunohistochemistry, and tumors with an MSH2 mutation will show loss of MSH2 and MSH6. By contrast, mutations in PMS2 or MSH6 lead to loss of only the affected protein (an exception is that MSH2 may be lost when both of its binding partners, MSH6 and MSH3, are lost). Moreover, immunohistochemistry can be performed on paucicellular specimens, as the samples obtained through core biopsy.

Combining the assessment of MSI status, MMR by IHC and MLH1 methylation increase the chance to identify “Lynch-like” endometrial cancer⁸¹. Endometrial cancer characterized by MSI has high neo-antigen expression, is more immunogenic than MSS tumors and has a higher level of TILs.

We will explore correlation between MSI and immune microenvironment (PD-L1 expression, CD3, CD4, and CD8) status in archival tissue and on baseline biopsy specimens and correlate it with patient outcome to define potential predictive biomarkers.

No data are available on evolution of microsatellite and immune microenvironment status in serial tumor samples in patients with different histological subtypes of endometrial cancer. We will explore the presence of differences in MMR status, PD-L1 expression, and immune cells infiltration between archival tissue and baseline biopsy.

At the time of randomization, MSI status defined using genomic analysis, or MMR status defined with IHC is to have been performed locally on archival tissue as per institutional standard, and will be used as a stratification factor. Subsequently, this will be centrally verified through IHC for MMR on archival tissue and on baseline biopsy (if sufficient tissue is available) for exploratory purposes.

2.4.2 MET amplification and mutation

Hyperactivation of hepatocyte growth factor (HGF) and MET pathway causes tumor cell proliferation and apoptosis inhibition, and is associated with antiangiogenic agent resistance^{11,51}. Hyperactivation of the HGF/MET pathway is present in 60% of endometrial cancer and is relevant in endometrioid and serous histology, and targeting this tyrosine kinase receptor inhibits both angiogenic and mitotic pathways^{14,52}.

Cabozantinib has shown preliminary activity⁵⁵ in endometrial carcinoma after progression from previous standard chemotherapy. No predictive biomarkers have been identified yet. Notably, in our previous study⁵⁵, MET pathway aberration was defined only on archival tissue and not at baseline biopsy.

In this study, we will assess the presence of MET mutation or amplification on biopsy specimens using RNA sequencing (RNAseq) performed through CIMAC. This will then be correlated with patient outcomes to explore its role as a predictive biomarker, and will also be compared with potential aberrations found in archival tissue, to explore the evolution of MET mutations/amplification following disease progression.

In renal cancer cells, association between MET pathway activation and expression of negative co-stimulatory immune proteins, such as PD-L1, has been found⁶⁰. We will explore the correlation between MMR status, MET aberrations, and the immune microenvironment in a population of patients with endometrial cancer with progressive disease following previous chemotherapy.

2.4.3 Whole Exome Sequencing (WES)

Endometrial carcinomas have been originally classified in two groups based on clinical, histological, and molecular features. Type I endometrioid tumors usually characterized by hormonal receptors expression, with the most common mutations found in PTEN, PI3K/AKT pathway, KRAS, CTNNB1, ARID1A, FGFR2, and with microsatellite instability (MSI) frequently found². The most common mutations in type II serous tumors are found in TP53, PI3KCA and PPP2R1A. There is a 25% incidence of ERBB2 amplification, but microsatellite instability is rare. TP53 has been also detected in high-grade endometrioid endometrial cancer and in carcinosarcoma. Carcinosarcoma has ERBB2 amplification and PI3KCA mutation in 27% and 42% of tumors, respectively².

We will assess the presence of somatic mutations using next generation sequencing (NGS; performed through CIMAC) on baseline tissue and correlate this with patient outcomes to identify potential biomarkers of response. We will also attempt to define clonal evolution of endometrial cancer by comparing the burden and type of somatic mutations at baseline and progression.

2.4.4 Definition of Immune-Markers

2.4.4.1 Tumor Tissue

In this study, we may assess PD-L1 expression, TILs (e.g. CD3, CD4 and C8+ cells) infiltration, and markers of tumor angiogenesis, on archival tissue and biopsy specimens. A comparative analysis will be performed to define potential clonal evolution following progression.

Identification of biomarkers able to predict activity of immune checkpoint inhibitors is needed to better select patients most likely to benefit from these treatments. To date, no definitive data are available to confirm the role of PD-L1 expression as a predictive biomarker of response. For this purpose, PD-L1 expression will be assessed on archival tissue and biopsy specimens by IHC, and correlated with patient outcome. Testing will be performed through the CIMAC at the Icahn School of Medicine at Mount Sinai.

Tumor microenvironments play a relevant role in favoring treatment sensitivity or resistance, representing a potential predictive biomarker. Presence and distribution of T cell immune infiltrates (regulatory T cells and cytotoxic T cells) will be analyzed on tissue specimens using several methods. Multiplex IHC (mIHC), performed through the CIMAC at the Icahn School of Medicine at Mount Sinai, will be used to assess TILs levels in archival tissue and biopsy specimens. Fresh samples from biopsies will be analyzed by flow cytometry and/or mass cytometry (CyTOF) to assess specific immune populations at the Translational Immunotherapy Laboratory- Princess Margaret Cancer Centre (Dr. Butler/Ohashi). Analysis will include effector T cells, B cells, NK cells, and myeloid subsets, as well as the expression of activation/exhaustion markers.

The antiangiogenic agent, cabozantinib, may potentially inhibit multiple tyrosine kinases implicated in endometrial cancer, leading to increased objective positive response to the immune checkpoint inhibitor, nivolumab. In this study, we seek to evaluate the clinical relevance of angiogenic markers in endometrial cancer, and investigate the therapeutic efficacy of targeting of receptor tyrosine kinases (i.e. MET, VEGFR2, FLT3, c-KIT, and RET) using cabozantinib in combination with nivolumab. Angiogenic markers will be assessed in archival tissue and biopsy specimens by mIHC performed through the CIMAC at the Icahn School of Medicine at Mount Sinai.

The diversity of T cells is determined by their T cell receptor (TCR) repertoire. Recently presented data have indicated that large clonal T-cell expansions were associated with inferior PFS and OS in B-cell lymphoma. Evaluating the importance of repertoire diversity in controlling endometrial cancer may elucidate why certain patients respond to therapy. In this study we will examine the prognostic impact of the TCR repertoire, assess the impact of the TCR repertoire on survival after single and combination therapy, examine the dynamics of the TCR repertoire after treatment with single and combination therapy, and investigate the relationship between intratumoral TCR repertoire and the tumor microenvironment. TCR sequencing (TCRseq) will be performed by Adaptive Biotechnologies in collaboration with the CIMACs.

When sample from baseline biopsy is limited, the priority will be: 1) PD-L1 expression; 2) TILs & vascularization markers mIHC; 3) WES; 4) RNAseq; 5) TCRseq; 6) immune markers on tumor in CyTOF/flow cytometry; 7) MMR status.

If enough archival tissue will be available, comparative analysis will be performed to explore changes in MMR status, PD-L1 and immune populations assessed with IHC. Priority will be: 1) PD-L1; 2) TILs & vascularization markers ; 3) MMR status.

Patients enrolled in arm B (single agent nivolumab) at the time of progression can be crossed-over to combination treatment with cabozantinib and nivolumab. A mandatory biopsy will be required to assess changes in immune cell infiltrates following treatment with nivolumab. Analysis will be performed according the same prioritization used for baseline tissue.

At the time of progression, all patients will be consented to have an optional tumor biopsy. The same analysis as on baseline biopsy will be performed for comparative analysis.

2.4.4.2 Peripheral Blood

An exploratory analysis of peripheral blood will be performed to phenotypically characterize cellular subsets such as effector lymphocytes, regulatory T cell and myeloid subsets. Analysis will be performed using flow cytometry and/or CyTOF analysis (as sample material allows). Assays will be conducted through both the CIMAC at the Icahn School of Medicine at Mount Sinai, and the Princess Margaret Cancer Centre (Translational Immunotherapy Laboratory; Dr. Butler/Ohashi). Panels include, but are not limited to, markers such as CD45RA, CD45RO (immune cells); CD3, CD4, CD8, FOXP3 (T-cell subsets), TCRgd (gamma-delta T-cells); NKp46 (NK cells), CD19 (B cells), CD11c, CD14, CD16, HLA-DR (myeloid cells); PD-L1, PD-1, TIGIT, CTLA-4, 4-1BB, CD133, CD33 (immune checkpoint); Fas, Granzyme B (cytotoxicity); CD27, CD28 (T-cell co-stimulation); CD25, CD127, Helios, ICOS, CD39 (Treg markers); CD103, CD69, CXCR3 (T-cell infiltration); and Ki67 (cell proliferation).

One approach to test whether tumors become more immunogenic as a result of immunotherapy is to determine the levels of selected soluble immune markers in patient serum or plasma. Analysis of the humoral immune response in peripheral blood can be done by antibody profiling, and by quantifying changes in other soluble analytes, such as cytokines. In this study, cytokine/antibody responses will be correlated with patient outcomes, differentially analyzed between mono- and combination therapies, and assess for dynamic changes as therapy progresses. Antibody titers will be assessed in plasma samples by enzyme-linked immunosorbent assay (ELISA)/Grand Serology, and cytokine levels will be determined using the O-link platform. Both assays will be performed through the CIMAC at the Icahn School of Medicine at Mount Sinai. Multiplex platforms, such as the Luminex platform, may also be used at Princess Margaret Cancer Centre (Translational Immunotherapy Laboratory; Dr. Butler/Ohashi) to measure chemokines/cytokines involved in pro-inflammatory innate responses such as $\text{INF}\alpha$.

Patients will be requested to have 3 blood samples collected (sodium heparin) for exploratory analysis at different time points:

- at baseline before starting treatment (prior to day 1 cycle 1);
- during treatment before being dosed: at cycle 1 day 15 (week 2), and at day 1 of each following cycle;
- and at the time of progression.

In other tumor types, preliminary data have shown that antiangiogenic agents might have a role in reversing the immune-suppressive microenvironment, increasing the activity of effector T cells and reducing regulatory T cells, supporting the rationale to combine immune therapy with antiangiogenic agents^{71,77}. In our study, we will assess the immune markers landscape at baseline and during treatment, correlate with outcome, and explore the differences between the two treatment arms (immune checkpoint alone versus immune checkpoint in combination with the antiangiogenic agent, cabozantinib).

3. PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients must have histologically or cytologically confirmed epithelial endometrial carcinoma. All histologies are accepted. Patients with diagnosis of endometrial carcinosarcoma will be enrolled in the exploratory cohort (arm C) and will receive combination of cabozantinib and nivolumab.
- 3.1.2 Patients must have advance, recurrent or metastatic endometrial cancer.
- 3.1.3 Patients must have radiological evidence of disease progression following the most recent treatment.
- 3.1.4 Patients must have measurable disease according RECIST v1.1 criteria.
- 3.1.5 Must have MS/MMR result available at time of registration. MS/MMR status is to be determined per local practice (i.e. IHC, PCR, or other methods).
- 3.1.6 Prior therapy: eligible subjects must have had at least one line of platinum-based chemotherapy. This may be adjuvant therapy or first line of cytotoxic therapy for metastatic disease. Prior hormonal therapy for metastatic/recurrent disease, prior targeted therapy, and prior radiotherapy are allowed. No maximum number of previous lines of chemotherapies. Concomitant chemo-radiation is not considered as previous line of systemic chemotherapy.
- 3.1.7 Availability of archival tissue for correlative analysis.
- 3.1.8 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of cabozantinib and nivolumab in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- 3.1.9 ECOG performance status 0-2 (see [Appendix A](#)).
- 3.1.10 Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count $\geq 1,500/\text{mcL}$
- platelets $\geq 100 \times 10^9/\text{L}$
-
- total bilirubin $\leq 1.5 \text{ ULN}$ (upper limit of normal), unless due to Gilbert's syndrome
- AST(SGOT)/ALT(SGPT) $\leq 3 \times$ institutional upper limit of normal
- creatinine $\leq 1.5 \text{ ULN}$
- OR
- creatinine clearance $\geq 50 \text{ mL/min/1.73 m}^2$ for patients with creatinine levels above institutional normal
- serum albumin $\geq 28 \text{ g/L}$
- lipase $\leq 2 \text{ ULN}$

- urine protein/ creatinine ratio (UPCR) ≤ 1
- prothrombin time (PT)/ International Normalized Ratio (INR) and partial thromboplastin time (PTT) test ≤ 1.3 ULN

3.1.11 Patient must have disease amenable to biopsy and must agree to have one baseline biopsy.

3.1.12 The effects of cabozantinib and nivolumab on the developing human fetus are unknown. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test at screening. WOCBP must agree to use adequate contraception (barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. WOCBP should use an adequate method to avoid pregnancy for 7 months after the last dose of investigational drug. Women must not be breastfeeding.

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

3.1.13 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. targeted therapy or antibodies) or radiotherapy within 4 weeks prior to the first dose of study treatment.
- 3.2.2 Patients who have not recovered from adverse events attributed to prior anti-cancer therapy (*i.e.* have residual toxicities $>$ Grade 1, except for alopecia, neuropathy, lymphocytopenia and other non-clinically significant adverse events).
- 3.2.3 Patients who are receiving any other investigational agents.
- 3.2.4 Patients should be excluded if they have had prior treatment with anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation. Previous treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2 is allowed and patients will be enrolled in the exploratory cohort (arm C) at the time of progression from last line of treatment (treatment with immune check point inhibitor does not have to necessary be the last line of treatment).
- 3.2.5 Patients should be excluded if they have had prior treatment with cabozantinib. Previous use of other antiangiogenic agents other than cabozantinib is allowed.

- 3.2.6 Any other active malignancy other than the endometrial cancer, that is progressing or requiring active treatment with the exception of basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of any site.
- 3.2.7 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because of the possible increased risk of bleeding if treatment with antiangiogenic agents is provided. Patients with history of brain metastases can enroll provided the brain metastases were removed and controlled with no radiological evidence within the past 6 months.
- 3.2.8 Patients requiring concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, antiplatelet agents (e.g. clopidogrel) or new oral anticoagulants. Low-dose aspirin (≤ 81 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
- 3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib or nivolumab.
- 3.2.10 Patients require chronic concomitant treatment of strong CYP450 3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St. John's Wort) or inhibitors (eg. ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil and conivaptan).

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/main-table/>; 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.

- 3.2.11 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 hemorrhage within 3 months before the first dose of study treatment.
- 3.2.12 The subject has radiographic evidence of cavitating pulmonary lesion(s).
- 3.2.13 The subject has tumor invading or encasing any major blood vessels.

- 3.2.14 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 XL184 (cabozantinib).
- 3.2.15 Subject with extensive pelvic mass at risk of fistulization, or history of bowel obstruction within 3 months prior to the proposed first dose of study treatment.
- 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

- 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.
 4. Other clinically significant disorders such as:
 - a. active infection requiring systemic treatment within 28 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 Known active human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) related illness, or hepatitis B or C infection.
- 3.2.18 Administration of a live vaccine within 4 weeks prior to start of protocol therapy.
- 3.2.19 Subjects with diagnosis of immunodeficiency or who are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The following are exceptions to this exclusion criteria: intranasal, inhaled, topical steroids, or local steroids injections (e.g. intra-articular injection); systemic corticosteroids at physiologic dose not to exceed 10 mg/day of prednisone or equivalent; steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

- 3.2.20 History of autoimmune disease, such as, but not restricted to: rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, ankylosing spondylitis, scleroderma, or multiple sclerosis requiring treatment within the last two years. Patients with vitiligo or diabetes are not excluded. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with recent history of thyroiditis. Subjects with remote history (greater than 5 years) of thyroiditis are not excluded.
- 3.2.21 Psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.22 The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.
- 3.2.23 Patient is not able to swallow pills.
- 3.2.24 Pregnant women are excluded from this study because XL184 and nivolumab are agents 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 and nivolumab, breastfeeding should be discontinued if the mother is treated with XL184 and nivolumab.

3.3 Cross-over Eligibility Criteria

Patients randomized to Arm B (nivolumab) will be allowed to cross over to the combination of cabozantinib and nivolumab as part of an exploratory cohort (Arm C) at time of progression, if they so choose.

Patients can only be crossed-over to Arm C if all the above inclusion and exclusion criteria are satisfied.

At time of cross over, the patient must also satisfy the following criteria:

- 3.3.1 Patient must provide a tumor biopsy at the time of progression on Arm B. If a patient does not have a tumor lesion amenable to biopsy or it has been unsafe for a biopsy to be performed, cross-over will not be allowed.

3.4 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research, unless a clear and compelling rationale and justification establishes, to the satisfaction of the funding Institute & Center (IC) Director, that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see <http://grants.nih.gov/grants/funding/phs398/phs398.pdf>.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iam>). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
HSP/GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < TBD >. For questions, please contact the RCR **Help Desk** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record is listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10104 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to <https://www.ctsu.org> and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-11030, and protocol #10104.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements for 10104 Site Registration

- Tracking System Training Requirement:
 - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
 - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
 - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
 - This training will need to be completed before the first patient enrollment at a given site.
 - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submissions must be made via the Regulatory Submission Portal: www.ctsuo.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

NCI CIRB Institutions: Submit model informed consent to the Central Office (Study Coordinator on protocol face page) for pre-approval prior to submitting to CTSU Regulatory Office. Once pre-approval is obtained, submit completed forms along with a copy of your IRB Approval, Model Informed Consent and ETCTN Specimen Tracking Training to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS. Sites will submit their IRB-approved local ICs and all future amended ICs to the CTSU Regulatory Office for tracking in RSS. The CTSU Regulatory Office will forward the IRB initial approval and accompanying local informed consent(s) to the Central Office (study coordinator on protocol face page) for documentation purposes. This also applies to future amendment approvals.

Non-CIRB US Institutions: Submit model informed consent to the Central Office (Study Coordinator on protocol face page) for pre-approval prior to submitting to your local IRB/REB. Once pre-approval is obtained, submit to your local IRB. Sites will submit their IRB/REB initial approval (accompanied by local IC) along with ETCTN Specimen Tracking Training; all future amendment approvals (accompanied by updated local IC if applicable); and continuing review approvals to the CTSU Regulatory Office for tracking in RSS. The CTSU Regulatory Office will forward the IRB initial approval and accompanying local informed consent to the Central Office (study coordinator on protocol face page) for documentation purposes. This also applies to future amendment approvals.

Canadian Institutions: Submit model informed consent to the Central Office (Study Coordinator on protocol face page) for pre-approval prior to submitting to your local IRB/REB. Once pre-approval is obtained, submit to your local IRB. Sites will submit their IRB/REB initial approval (accompanied by local IC) along with ETCTN Specimen Tracking Training; all future amendment approvals (accompanied by updated local IC if applicable); and continuing review approvals to the Central Office. The Central Office will submit copies of IRB approval documentation, ICs (and QIU and CTSI for Canadian sites) to the CTSU Regulatory Office for tracking in the RSS. This also applies to future amendment approvals.

4.2.4 Checking Site Registration Status

Sites can check the status of their registration packets by querying the Site Registration sub-tab of the members' section of the CTSU Web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.* CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 Patient Enrollment Instructions

To register a patient, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Central Office Coordinator:

- Registration Checklist
- Signed patient consent form
- HIPAA authorization form, if applicable
- Site staff with the appropriate roles will reserve slots using IWRS (<https://open.ctsu.org/>)
- The Central Office will receive notification via the IWRS when a slot has been reserved. An email will be sent from the Central Office Coordinator to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as ‘pending approval’ in the system until the site sends the above mentioned documents to the Central Office Coordinator for review and confirmation of eligibility.
- Once the Registration has been reviewed, the Central Office Coordinator will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the Central Office Coordinator will update the spot to ‘reserved’ in IWRS.
- The site can now enroll the patient into the study in OPEN

4.3.4 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- Only biospecimens to be analyzed by CIMAC at timepoints specified in [Section 9.2](#) will be submitted to the ETCTN Biorepository and entered into the ETCTN Specimen Tracking System (STS).
- The system is accessed through special Rave user roles: “CRA Specimen Tracking” for data entry at the treating institutions and “Biorepository” for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in [Section 9.3](#).

4.3.5 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator. 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. 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) and the patient is registered in OPEN. Clinical drug requests can be expedited overnight Monday-Thursday (US) and Monday-Wednesday (Canada) when sites provide expedited courier information in OAOP."

5. TREATMENT PLAN

This is an open-label phase 2 randomized trial enrolling women with advanced, recurrent or metastatic endometrial cancer, that has progressed after at least one line of platinum based chemotherapy. All histologies are allowed. Patients with endometrial carcinosarcoma will be enrolled in an exploratory cohort (arm C) receiving combination of cabozantinib and nivolumab. Patients will be randomized to receive a combination of cabozantinib and nivolumab (arm A) or nivolumab alone (arm B) in a 2:1 ratio and with stratification according MS/MMR status defined locally as per standard guidelines. A mandatory biopsy is required at baseline, before starting the treatment (≤ 28 days and ≥ 7 days before starting treatment). Patients enrolled in arm B, will be offered to cross-over to combination treatment at the time of progression and another biopsy (if feasible) will be required before starting combination treatment and patients will be considered part of an exploratory cohort following cross-over. Patients that have previously received at any time anti-PD-1, PD-L1 or PD-L2 for the treatment of endometrial cancer, can be enrolled in arm C at the time of progression from last treatment and will receive combination of cabozantinib and nivolumab. Patients enrolled in arm C will not be considered for statistical analysis.

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, 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 (Cabozantinb)

XL184 will be dosed continuously (once daily) on a 28-day cycle starting at 40 mg orally once per day. Skipped/missed doses will not be made up if discovered to have been missed within 12 hours of the next planned dose.

Dose Level	Dose XL184 (Cabozantinib)
Level 1	40 mg daily orally
Level -1	20 mg daily orally

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

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. A sample template can be found in Appendix D.

5.1.2 Nivolumab

Nivolumab will be given intravenously every two weeks (± 2 days) at a flat dose of 240 mg, on day 1 and 15 of a 28 day cycle. Patients should not be dosed within 12 days of their previous dose. After 4 cycles, nivolumab will be administered at the dose of 480 mg IV every 4 weeks, if well tolerated. The treating investigator may choose to continue dosing at 240 mg at day 1 and 15 of a cycle if they feel it is in the patient's best interest.

There will be no dose modifications allowed.

Nivolumab is to be administered as a 30-minute IV infusion (± 10 minutes), using a volumetric pump with a 0.2 micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

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. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients.

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 investigator's discretion.

5.2.1.2 Other Medications

Subjects must be instructed to inform the investigators of the current or planned use of 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 for XL184 (cabozantinib)

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]/K_i 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 approximately an 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 (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 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 (<http://medicine.iupui.edu/CLINPHARM/ddis/main-table>).

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 is prohibited 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. Treatment with other drugs associated with QTc prolongation should be avoided when treating subjects on cabozantinib (see <http://www.qtdrugs.org>). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

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 allowed.

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 for XL184 (cabozantinib).

5.3 Preliminary Safety Assessment

Once the first 6 patients receiving combination of cabozantinib and nivolumab (arm A and arm C carcinosarcoma patients only) have completed Cycle 1, a preliminary safety assessment will be conducted to look at toxicities considered unrelated to disease or disease processes, but related to either/both of nivolumab and/or cabozantinib. Patients will be discontinued from protocol therapy if any of the following toxicities occur:

- 1) Hematological toxicity \geq Grade 4 present for more than 7 days, including infection with febrile neutropenia
- 2) Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding
- 3) Non-hematological toxicity \geq Grade 3 which is unexpected in severity and/or duration compared to the known safety profiles of either cabozantinib or nivolumab when used as single agents, and that cannot be reduced to \leq Grade 2 despite optimized supportive care.
- 4) Grade ≥ 3 total bilirubin, hepatic transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or alkaline phosphatase (ALP) lasting >48 hours.
- 5) Changes in liver function tests (LFTs) consistent with the definition of Hy's Law
- 6) Any other toxicity that is clinically significant and/or unacceptable that does not respond to supportive care, results in a disruption of dosing schedule of more than 7 days, or is judged to be of concern by the Investigator in collaboration with the Principal Investigator.

If 0 to 1 patients develop any of the toxicities mentioned above during their first cycle, the study will continue with a 40 mg daily dose of XL184 without pause. If 2 or more of the 6 patients have any of the above mentioned toxicities during cycle 1, a dose de-escalation to 20 mg daily dose of XL184 will be applied for the remainder of the study. The study will be put on hold until such time as a protocol amendment is made specifying this dose for the remaining patients accrued to the trial.

5.4 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 (radiological or clinical)
- Intercurrent illness that prevents further administration of treatment
- Toxicity within Cycle 1 as described in Section 5.3^a
- Unacceptable adverse event(s)^a
- 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

- Patient non-compliance
- Any dosing interruption lasting >4 weeks, with the following exception: Dosing interruptions >4 weeks that occur for non-drug-related reasons may be allowed if approved by the Study Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting >4 weeks, the Study Investigator must be consulted
- Pregnancy
 - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during study participation.
 - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g. female condom) during the course of the study and for 7 months following discontinuation of study treatment.

^a If a patient enrolled in arm A or arm C is experiencing a DLT or adverse event related to cabozantinib, at the investigator discretion treatment with nivolumab can continue. If treatment is discontinued before first radiological assessment, the subject will be replaced.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.5 Duration of Follow Up

The patient will have a 30-37 day follow-up visit from the day it was decided to discontinue treatment. This visit is to document all new or ongoing treatment-related toxicities. If the patient discontinued treatment for reasons other than disease progression, they will be followed until disease progression as defined by RECIST 1.1. All patients will continue to be followed every 8 weeks (+/- 1 week) thereafter by phone or via clinic visit until all toxicities considered to be related to one or both study drugs are <grade 2, returned to baseline, stabilized in the opinion of the investigator, or deemed to be no longer attributable to one or both study drugs. Once adverse event follow-up has been completed, patients will be followed every 12 weeks (+/- 2 weeks) by phone, clinic visit, or medical records review for survival status.

5.6 Criteria for Removal from Study

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

- Patient withdrawal
- Patient death
- Termination of the study by Principal Investigator, or regulatory agency

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

6.1 XL184 (Cabozantinib)

Dose Level	Dose XL184 (Cabozantinib)
Level 1	40 mg daily orally
Level -1	20 mg daily orally

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, proteinuria, 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 section 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 XL184 (Cabozantinib) Investigator's Brochure.

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

CTCAE Version 5 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue XL184 at the current dose level.
Grade 2:	
Grade 2 AEs considered related to XL184 that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue XL184 at the current dose level.
Grade 2 AEs considered related to XL184 that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Dose reduce <ul style="list-style-type: none"> If the AE does not resolve to Grade ≤ 1 or baseline in 7 to 10 days or worsens at any time, XL184 dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. If the AE resolves to Grade ≤ 1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to XL184 which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	<ul style="list-style-type: none"> Interrupt XL184 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, XL184 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, XL184 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 \leq Grade 1 or baseline, and resume treatment with a dose reduction
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.
<i>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.</i>	

Table 6-2. General Approach to the Management of XL184 (Cabozantinib)-Related Hematologic Adverse Events.

CTCAE Version 5 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days	Interrupt XL184 treatment until resolution to Grade ≤ 1 , and resume XL184 treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding	Interrupt XL184 treatment until platelet count is $\geq 100,000/\text{mm}^3$, and resume XL184 treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt XL184 treatment until recovery of ANC to Grade ≤ 1 and temperature to $\leq 38.0^\circ\text{C}$ and resume XL184 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 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.
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.
<p>ANC, absolute neutrophil count; LLN, lower limit of normal</p> <p>Neutropenia: Grade 1 ($\text{LLN} \leq \text{ANC} < 1.5 \times 10^9/\text{L}$; Grade 2 ($1 \times 10^9/\text{L} \leq \text{ANC} < 1.5 \times 10^9/\text{L}$), Grade 3 ($0.5 \times 10^9/\text{L} \leq \text{ANC} < 1 \times 10^9/\text{L}$), Grade 4 ($\text{ANC} < 0.5 \times 10^9/\text{L}$).</p> <p>Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).</p> <p>Thrombocytopenia: Grade 1 (Platelet count $< \text{LLN} - 75 \times 10^9/\text{L}$); Grade 2 (Platelet count $< 75.0 - 50.0 \times 10^9/\text{L}$); Grade 3 (Platelet count $\leq 50 - 25 \times 10^9/\text{L}$); Grade 4 (Platelet count $< 25 \times 10^9/\text{L}$).</p>	

Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

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, and is to be prescribed to subjects at the start of study therapy, to be taken PRN. Subjects should be instructed to start loperamide immediately at the first signs of poorly formed or loose stool or an increased frequency in bowel movements. 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 XL184 exposure). 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 XL184. In general, it is recommended that subjects with elevated levels 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 XL184 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 XL184 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 XL184 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 XL184.
Grade 3	Interrupt XL184 treatment and monitor with at least twice weekly LFTs until Grade ≤ 2 . Then continue with at least weekly LFTs until resolution to Grade ≤ 1 . XL184 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 XL184 as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but $\leq 3.0 \times$ ULN (i.e. Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are $\leq 5.0 \times$ ULN	Continue XL184 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 XL184
≥ 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 $\leq 20.0 \times$ 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 XL184.
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..

XL184 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 XL184 should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR $< 1.5 \times$ ULN, total bilirubin $< 1.5 \times$ ULN, aminotransferases \leq baseline grade).

Subjects must have XL184 permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation $> 2 \times$ 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). 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 XL184. 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	<ul style="list-style-type: none"> • Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, XL184 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	<ul style="list-style-type: none"> • Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, XL184 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	<ul style="list-style-type: none"> Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	<ul style="list-style-type: none"> Interrupt treatment Monitor lipase and amylase twice weekly Upon resolution to Grade ≤ 1 or baseline, XL184 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 XL184 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 XL184-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 XL184 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	Reduce XL184 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. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, affects self-care, or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was only reduced but not interrupted, treatment may continue at the reduced dose. If the dose was only interrupted but not reduced, then treatment may be restarted upon resolution to Grade 0 or Grade 1 at one dose level lower. Cabozantinib treatment may be continued if PPES is tolerated.
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 XL184; 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. Treatment with cabozantinib may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at significant risk that outweighs the benefit of resuming treatment per discretion of the investigator, and with one dose level reduction. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed. 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 XL184. XL184 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 XL184 clinical studies.

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with XL184 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. XL184 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 XL184

Criteria for Dose Modifications	Treatment/ XL184Dose 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	<ul style="list-style-type: none"> • Increase antihypertension therapy (i.e. increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of XL184 • 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 XL184 should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	<ul style="list-style-type: none"> • Reduce XL184by one dose level. • Increase antihypertension 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, XL184 should be interrupted.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	<ul style="list-style-type: none"> • Interrupt treatment with XL184 • 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 XL184 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, XL184 should be interrupted.
Hypertensive crisis or hypertensive encephalopathy	Discontinue all study treatment
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria	

Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. The below table provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Management of Proteinuria Associated with Cabozantinib

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1 (mg/mg) (≤ 113.1 mg/mmol)	<ul style="list-style-type: none"> No change in treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	<ul style="list-style-type: none"> Consider confirming with a 24-hour protein assessment within 7 days No change in study treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting 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 interruption. Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of 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)	<ul style="list-style-type: none"> Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein. <ul style="list-style-type: none"> If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and 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	<ul style="list-style-type: none"> Discontinue cabozantinib 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 XL184. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating XL184 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 XL184.
- 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 XL184 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 or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from XL184 treatment.

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. XL184 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 XL184. 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 XL184.

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 XL184 treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with XL184.

Treatment with XL184 must be interrupted for any wound healing complication which needs medical intervention. Treatment with XL184 can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. XL184 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, XL184 should be stopped at least 28 days (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 XL184 on thyroid function. Preliminary data indicate that XL184 affects thyroid function tests (TFTs) in a high number of subjects (see XL184 Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with XL184. 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 XL184 is required. XL184 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 XL184, 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 XL184. If clinically possible, treatment with XL184 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 XL184 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 CYP3A4 inhibitors (which may increase XL184 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 XL184 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.

If treatment with cabozantinib will be interrupted due to drug related adverse event, at investigator discretion and after discussion with the Principal Investigator, treatment with nivolumab can be continued and study procedures will follow regular calendar.

6.2 Nivolumab

No dose reduction is allowed.

Nivolumab adverse event management

Please refer to the Nivolumab Investigator Brochure or Appendix C of the protocol for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended.

<u>Skin Rash and Oral Lesions</u>	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose *
Grade 2	Hold* until 1 ≤ Grade resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

<u>Liver Function</u> <u>AST, ALT,</u> <u>Bilirubin</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Hold until UNL or baseline. Resume at same dose level.
Grade 2	Hold until UNL or baseline. Resume at same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

<u>Diarrhea/ Colitis</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Hold until baseline. No change in dose
Grade 2	Hold until baseline. No change in dose
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients are to be prescribed loperamide at the start of study therapy, to be taken PRN, and instructed to talk it at the first signs of diarrhea. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes <i>C. diff</i> , acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

<u>Pancreatitis</u> <u>Amylase/Lipase</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Hold dose until baseline. Resume at same dose level if asymptomatic
Grade 2	Hold until baseline. Resume at same dose level if asymptomatic
Grade 3	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Grade 4	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

<u>Pneumonitis</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO ₂ . Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

<u>Other GI N-V</u>	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

<u>Fatigue</u>	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level
Grade 4	Off protocol therapy
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

<u>Neurologic events</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. # Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy)
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

<u>Endocrine</u> <u>Hypophysitis</u> <u>Adrenal</u> <u>Insufficiency</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Asymptomatic TSH elevation. Hold pending evaluation, endocrine consult
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Off study treatment.
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

<u>Renal</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Continue treatment. Monitor creatinine weekly until normalization..
Grade 2	Hold until ≤ Grade 1. Monitor creatinine every 2-3 days. Consider 0.5-10 mg/kg/day. If ≤ Grade 1 taper steroids and consider restarting treatment. See Renal Management Algorithm.
Grade 3	Hold until ≤ Grade 1. Monitor creatinine every 2-3 days. Administer 0.5-10 mg/kg/day. Consider nephrologist consult and kidney biopsy. If ≤ Grade 1 taper steroids and consider restarting treatment. See Renal Management Algorithm .
Grade 4	Off treatment. Treatment as per Grade 3 toxicity.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
Recommended management see Renal Management Algorithm.	

<u>Infusion reaction</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Infusion can be slowed or interrupted and the restarted when symptoms will improve. See section 6.2.1 for details and indication for premedication.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level at following cycle with premedication as detailed in section 6.2.1.
Grade 3	Off treatment
Grade 4	Off treatment
For details refer to section 6.2.1	
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	

<u>Fever</u>	Management/Next Dose for Nivolumab
≤ Grade 1	Evaluate and continue at same dose level
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See section 6.2.1. <i>infusion reactions</i>	

<u>ALL OTHER EVENTS</u>	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.
- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

If treatment is delayed >4 weeks for an adverse event the patient must be permanently discontinued from study therapy.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results. Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2week observation period without further symptoms at the discretion of the PI or investigator.

Please refer to the below table for drug modifications for cardiomyopathy myocarditis

Cardiac *	Management/Next dose for BMS-936558 (Nivolumab)
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
<p>* Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin</p> <p>** Patients with evidence of myositis without myocarditis may be treated according as “other event”</p> <p>Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.</p>	

6.2.1 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated) Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [*e.g.* antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours), and no further nivolumab will be administered at that visit.

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction),

Grade 3 symptoms: prolonged [*i.e.* not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [*e.g.* renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV

with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

For patients enrolled in arm A and C: if treatment with nivolumab will be interrupted due to drug related adverse event, at the investigator discretion and after discussion with the Principal Investigator, treatment with cabozantinib can be continued and study procedures will follow regular calendar.

If one of the two drugs will be permanently interrupted before the first radiological assessment, subject will be replaced.

IMPORTANT NOTE: some toxicities could be commonly seen with both drugs (e.g. diarrhea, liver toxicity, skin rash). If necessary according to severity of drug reaction, both drugs will be hold and specific supportive treatment provide. Maximum effort will be required to establish a drug causality, when feasible. Dose reduction and/or drug interruption will be considered according the type and severity of the adverse event. If the causality of an AE will not be possible to assigned to one drug, the AE will be considered related to both drugs.

6.3 Criteria to Resume Treatment

For non-autoimmune or non-inflammatory events patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Evaluation to exclude any additional immune mediated events endocrine, GI, and liver / pancreas function as clinically indicated must be made prior to restarting.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol the treatment should resume at the earliest convenient point that is within the 4-week delay period.

For patients treated with high dose steroids for immune-related AEs:
Must resolve to baseline within 4 weeks of treatment

Must be off steroids for at least 2 weeks with no recurrence or new immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing

immune activation and should require permanent discontinuation of nivolumab. After discussion with the Principal Investigator a physiological dose of steroids may be allowed (≤ 10 mg qd of oral prednisone or equivalent).

If one of the two drugs (arm A and C) will require permanent discontinuation, the other investigational agent could be resumed or continued at the investigational discretion and after discussion with the PI of the study.

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 (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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.

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.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for Nivolumab

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726)

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 2069 patients.* Below is the CAEPR for Nivolumab.

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 2.4, December 2, 2020¹

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr 3)</i>
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade ²	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency ³		
	Hyperthyroidism ³		
	Hypophysitis ³		
	Hypothyroidism ³		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia) ³	
		Eye disorders - Other (Graves ophthalmopathy) ³	
		Eye disorders - Other (optic neuritis retrobulbar) ³	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 2)</i>
	Colitis ³		
		Colonic perforation ³	
	Diarrhea		<i>Diarrhea (Gr 3)</i>
	Dry mouth		<i>Dry mouth (Gr 2)</i>
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		<i>Nausea (Gr 2)</i>
	Pancreatitis ⁴		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 3)</i>
	Fever		<i>Fever (Gr 2)</i>
	Injection site reaction		<i>Injection site reaction (Gr 2)</i>
HEPATOBIILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction ³	
		Autoimmune disorder ³	
		Cytokine release syndrome ⁵	
		Immune system disorders - Other (GVHD in the setting of allotransplant) ^{3,6}	
		Immune system disorders - Other (sarcoidosis) ³	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction ⁷		
INVESTIGATIONS			
	Alanine aminotransferase increased ³		<i>Alanine aminotransferase increased³ (Gr 3)</i>
	Aspartate aminotransferase increased ³		<i>Aspartate aminotransferase increased³ (Gr 3)</i>
	Blood bilirubin increased ³		<i>Blood bilirubin increased³ (Gr 2)</i>
	CD4 lymphocytes decreased		<i>CD4 lymphocyte decreased (Gr 4)</i>
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		<i>Lymphocyte count decreased (Gr 4)</i>
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	<i>Hyperglycemia (Gr 2)</i>

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis) ³	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy ³	
		Facial nerve disorder ³	
		Guillain-Barre syndrome ³	
		Myasthenia gravis ³	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis) ³	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis) ³	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome ³	
RENAL AND URINARY DISORDERS			
		Acute kidney injury ³	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion ³		
	Pneumonitis ³		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia) ³	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme ³	
	Pruritus ³		<i>Pruritus³ (Gr 2)</i>
	Rash maculo-papular ³		<i>Rash maculo-papular³ (Gr 2)</i>
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome) ³		
	Skin hypopigmentation ³		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

¹This 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.

²Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

³ Nivolumab being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

⁴Pancreatitis may result in increased serum amylase and/or more frequently lipase.

⁵Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

⁶Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

⁷Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBIILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic

microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab 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.

7.1.1.2 CAEPR for XL184 (Cabozantinib)

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 3219 patients. Below is the CAEPR for XL184 (Cabozantinib).

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 2.4, December 17, 2018¹

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Hypothyroidism		<i>Hypothyroidism (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 3)</i>
	Constipation		<i>Constipation (Gr 2)</i>
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Dry mouth		<i>Dry mouth (Gr 2)</i>
	Dyspepsia		<i>Dyspepsia (Gr 2)</i>
		Gastrointestinal fistula ²	
		Gastrointestinal hemorrhage ³	
		Gastrointestinal perforation ⁴	
	Mucositis oral		<i>Mucositis oral (Gr 3)</i>
Nausea			<i>Nausea (Gr 3)</i>
	Oral pain		<i>Oral pain (Gr 2)</i>
Vomiting			<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			<i>Fatigue (Gr 3)</i>
INFECTIONS AND INFESTATIONS			
	Infection ⁵		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased (Gr 3)</i>
	Aspartate aminotransferase increased		<i>Aspartate aminotransferase increased (Gr 3)</i>
	Lipase increased		<i>Lipase increased (Gr 4)</i>
	Platelet count decreased		<i>Platelet count decreased (Gr 3)</i>
Weight loss			<i>Weight loss (Gr 3)</i>
METABOLISM AND NUTRITION DISORDERS			
Anorexia			<i>Anorexia (Gr 3)</i>
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			<i>Dysgeusia (Gr 2)</i>

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		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)
	Hair color changes		Hair color changes (Gr 1)
Palmar-plantar erythrodysesthesia syndrome			Palmar-plantar erythrodysesthesia syndrome (Gr 3)
	Rash maculo-papular		Rash maculo-papular (Gr 3)
VASCULAR DISORDERS			
Hypertension			Hypertension (Gr 3)
	Thromboembolic event ⁹		

¹This 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.

²Gastrointestinal 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.

³Gastrointestinal 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.

⁴Gastrointestinal 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.

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

⁶Pneumothorax 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.

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism

EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBIILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); 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; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hyponatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive);

Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

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; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; 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.

7.2 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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://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 7.1.1.

- **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.

7.3 Expedited Adverse Event Reporting

- 7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (<https://eapps-ctep.nci.nih.gov/ctepaers>). 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 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). 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.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

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

Note: Due to the relatively high incidence of perforation in patients treated with XL184 (cabozantinib) monotherapy, all incidents of perforation, regardless of grade, should be reported to CTEP-AERS.

Note: A death on study requires both routine and expedited reporting, regardless of causality. 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.

Phase 1 and Early Phase 2 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 electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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 submitted electronically 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 electronically within 10 calendar days of learning of the AE.

¹Serious 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

²For 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

7.4 Routine Adverse Event Reporting

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

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 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 expeditiously 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 outlined in each protocol.

7.7 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 AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

8.1.1 Nivolumab (NSC #748726)

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume infused must not exceed 4mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage: Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications:

Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

Availability

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

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

8.1.2 XL184 (Cabozantinib) (NSC #761968)

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

Other Names: Cabozantinib s-malate, EXEL-7184, EXEL-02977184, Cabometyx®

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, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are VEGFR3, RET, AXL, KIT, TIE-2, FLT-3, ROS1, and RON.

How Supplied: XL184 is supplied by Exelixis and distributed by the DCTD. XL184 is available in 20 mg.. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg of cabozantinib. The 20 mg tablets have a round shape and they are packaged as 30 tablets per bottle.

XL184 should be dispensed in its original container; however, XL184 tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours. It can also be repackaged in a pharmacy dispensing bottle with expiration date not to exceed 7 days.

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, 20⁰ to 25⁰C, though temperature excursions to 15 °C or 30 °C are permitted.

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; i.e. do not eat 2 hours before or 1 hour after each dose of XL184. Do not crush or chew. Missed or skipped doses are not to be made up.

Potential Drug Interactions:

CYP450 isozymes:

In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. In healthy volunteers, XL184 AUC increased 38% with co-administration of ketoconazole, a strong inhibitor of CYP3A4, and decreased by 77% with a strong CYP3A4 inducer rifampin. Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications.

[**Note:** Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.]

XL184 is a noncompetitive inhibitor of CYP2C8 ($K_{iapp} = 4.6 \mu\text{M}$), a mixed-type inhibitor of both CYP2C9 ($K_{iapp} = 10.4 \mu\text{M}$) and CYP2C19 ($K_{iapp} = 28.8 \mu\text{M}$), and a weak competitive inhibitor of CYP3A4 (estimated $K_{iapp} = 282 \mu\text{M}$) in human liver microsomal (HLM). IC_{50} values $>20 \mu\text{M}$ were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2:

In vitro data indicate that XL184 is an inhibitor of P-glycoprotein transport activity ($\text{IC}_{50} = 7.0 \mu\text{M}$). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g. fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.).

XL184 is also a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, emtricitabine.

Protein bound:

XL184 is highly protein bound ($\geq 99.9\%$). Use caution when coadministering 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.

Antacids, H₂-blockers, PPIs:

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 allowed.

QTc prolongation:

Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

Potential Food Effect

A high fat meal increased both XL184 C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions; therefore, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each XL184 dose).

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. Refer to the protocol for management of adverse events.

Availability

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

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 Agent Ordering

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. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

Starter supplies are not being provided. Clinical drug requests can be expedited overnight Monday-Thursday (US) and Monday-Wednesday (Canada) when sites provide expedited courier information in OAOP.”

8.1.3.2 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an “active” account status and a “current” password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:
<https://ctepcore.nci.nih.gov/OAOP>
- CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Table 9.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	<ul style="list-style-type: none"> Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)¹ <p>If a block is not available, then submit:</p> <ul style="list-style-type: none"> 40 unstained, 4-5 µm, charged, air-dried 	ETCTN Biorepository
Baseline		
	<ul style="list-style-type: none"> 2 tumor cores processed to an FFPE² block 	ETCTN Biorepository
	<ul style="list-style-type: none"> 2 tumor cores in saline (UHN only) or RPMI + 2% FBS (non-UHN) 	Princess Margaret Cancer Centre
	<ul style="list-style-type: none"> 2 mL whole blood in purple top EDTA tube³ 	ETCTN Biorepository
C1D1 (pre-dose)		
	<ul style="list-style-type: none"> 30 mL blood in green top sodium heparin vacutainers (3 x 10 mL) Or 30 mL of blood in green top sodium heparin vacutainers (3 x 10 mL) processed to: <ul style="list-style-type: none"> Plasma (8 x 1 mL, frozen) PBMCs (5 x10⁶ per aliquot, cryopreserved)⁷ PBMC cell pellet (snap-frozen)⁴ 	Princess Margaret Cancer Centre
C1D15		
	<ul style="list-style-type: none"> 30 mL blood in green top sodium heparin vacutainers (3 x 10 mL) Or 30 mL of blood in green top sodium heparin vacutainers (3 x 10 mL) processed to: <ul style="list-style-type: none"> Plasma (8 x 1 mL, frozen) PBMCs (5 x10⁶ per aliquot, cryopreserved) 	Princess Margaret Cancer Centre
D1 Each Subsequent Cycle⁶		
	<ul style="list-style-type: none"> 30 mL blood in green top sodium heparin vacutainers (3 x 10 mL) Or 	Princess Margaret Cancer Centre

	<ul style="list-style-type: none"> 30 mL of blood in green top sodium heparin vacutainers (3 x 10 mL) processed to: <ul style="list-style-type: none"> Plasma (8 x 1 mL, frozen) PBMCs (5 x10⁶ per aliquot, cryopreserved)⁷ 	
Progression		
	<ul style="list-style-type: none"> 2 tumor cores processed to an FFPE block² 	ETCTN Biorepository
	<ul style="list-style-type: none"> 2 tumor cores in saline (UHN only) or RPMI + 2% FBS (non-UHN)⁵ 	Princess Margaret Cancer Centre
	<ul style="list-style-type: none"> 30 mL blood in green top sodium heparin vacutainers (3 x 10 mL) Or 30 mL of blood in green top sodium heparin vacutainers (3 x 10 mL) processed to: <ul style="list-style-type: none"> Plasma (8 x 1 mL, frozen) PBMCs (5 x10⁶ per aliquot, cryopreserved)⁷ 	Princess Margaret Cancer Centre
Cross-Over (If applicable)		
	<ul style="list-style-type: none"> 2 tumor cores processed to an FFPE block² 	ETCTN Biorepository
	<ul style="list-style-type: none"> 2 tumor cores in saline (UHN only) or RPMI + 2% FBS (non-UHN) 	Princess Margaret Centre
	<ul style="list-style-type: none"> 30 mL blood in green top sodium heparin vacutainers (3 x 10 mL) Or 30 mL of blood in green top sodium heparin vacutainers (3 x 10 mL) processed to: <ul style="list-style-type: none"> Plasma (frozen) PBMCs (cryopreserved)⁷ 	Princess Margaret Centre
<p>¹For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If pathology reports are not available, please complete the Pathology Verification Form provided in Appendix G.</p> <p>²For new biopsies, a copy of the radiology and operative reports from the tissue removal procedure must be sent with the tissue to the ETCTN Biorepository. If available, upload the corresponding pathology reports to Rave. If pathology reports are not available, please complete the Pathology Verification Form provided in Appendix G.</p> <p>³ Germline blood for CIMAC analysis may be collected at baseline (preferred), or at any time. Every effort should be made to obtain ETDA whole blood from previously enrolled patients. In cases where this is not possible to obtain, the snap frozen PBMC cell pellet, or adjacent normal tissue from baseline biopsy or archival tissue, may be used for CIMAC analysis.</p> <p>⁴ Snap-frozen cell pellet will be shipped from collecting sites to Prince Margaret Cancer Centre.</p>		

From there it will be batch shipped to the ETCTN Biorepository for distribution to the CIMAC Laboratory.

⁵Optional

⁶Once received and processed at Princess Margaret Cancer Centre, the C2D1 and C4D1 PBMC samples will be transferred to CIMAC for analysis.

⁷Of the PBMC samples collected at the CIMAC specified timepoints (pre-dose C1D1, C2D1, C4D1, Progression and Cross-Over, 1 aliquot of the cryopreserved PBMC sample will be transferred to CIMAC. The remaining aliquots will be analyzed at Princess Margaret Cancer Centre.

9.2 Specimen Collection

9.2.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria should be met:

- Tissue collected within 6 months prior to registration is preferred, older samples are acceptable.
- Formalin-fixed paraffin-embedded tumor tissue block(s) or slides must be submitted. The optimal block contains 30% tumor. Specimen size preference is as follows:
 - Surface area: 25 mm² is optimal. Minimum is 5 mm².
 - Volume: 1 mm³ is optimal. Minimum volume is 0.2 mm³, however the success of DNA extraction decreases at suboptimal tissue volume.

For analysis on archival FFPE tissue, blocks are preferred. However, if an existing block cannot be submitted, the following are requested, if available:

- 40 unstained sections, 4-5 µm thick, mounted on positively charged slides, and air-dried.

Ship archival specimens to the ETCTN Biorepository. Refer to Section 9.3.1 for labeling instructions. Ensure that the appropriate information is entered into the specimen tracking system (STS), see Section 9.3.

9.2.2 Fresh Biopsy Collection Procedure

- A fresh tumor biopsy should be collected -28 to -7 days for all patients before the start of treatment. An optional tumor biopsy may be collected at the time of progression from consenting patients.
- Patients who progress on Arm B (single agent nivolumab) who wish to cross over to cabozantinib and nivolumab combination are required to provide this biopsy before starting the combination treatment.
- Collect the biopsy with an 18-gauge core needle using standard surgical techniques.
- Lesions will be assessed by the radiologist or clinician performing the biopsy.
- The biopsy will be performed using standard surgical technique for visible lesion or under image guidance, either ultrasound or computed tomography (CT), if deemed necessary by the radiologist.
- If possible, obtain 3 to 4 cores. The first and second cores should be placed in 10% neutral

buffered formalin and processed into a FFPE block and shipped to the ETCTN Biorepository per Section 9.2.3. Cores 3 and 4 should be immersed in sterile RPMI with 2% FBS (non-UHN sites) or sterile saline (UHN only) and shipped to the Princess Margaret Cancer Centre per Section 9.2.4.

See Section 9.3.1 for labeling instructions.

9.2.3 Formalin-Fixed Tumor Biopsies

1. Immediately after collection, immerse the core in 10% buffered formalin. Handle the core with care to avoid crushing or damaging the tissue.
2. Record the date and time of the biopsy and the time placed in formalin on the Fresh Tumor Tissue Specimen Requisition (Appendix C in the Lab Manual).
3. Fixate in formalin for 12 – 24 hours.
4. Record the number of hours the tissue was fixed in formalin on the requisition.
5. Tumor specimens should be embedded in paraffin according to your institution's procedures.
6. After embedding, label the paraffin block according to Section 9.3.1.
7. Enter the appropriate information into the specimen tracking system (STS), see Section 9.3.
8. Ship the FFPE block to the ETCTN Biorepository.
9. Samples collected prior to protocol amendment version 5 must be entered into the ETCTN Specimen Tracking System and re-labeled according to Section 9.3 below before shipment.

9.2.4 Fresh Tumor Biopsies (for Immune Profiling)

Processing instructions for Non-University Health Network (UHN) sites:

1. Prepare a 50 mL conical tube with 30 mL of RPMI 1640 with 2% FBS.
2. Label the tube with the protocol, patient ID, patient initials, study visit, as well as the date of the collection.
3. Record the date and time of collection on the Fresh Tumor Tissue Specimen Requisition (Appendix C in the Lab Manual).
4. Immediately submerge tissue in RPMI solution.
5. Keep sample at 4°C until shipment.
6. Ship refrigerated (Monday to Wednesday) to the Correlative Studies Program at The Princess Margaret Cancer Centre.
7. If the biopsy is collected on a Thursday or Friday, place cores in formalin and process into a separate FFPE block as described section 9.2.3 above.

Processing instructions for UHN Only:

1. Prepare a 50 mL conical tube with 30 mL of sterile saline (0.9% sodium chloride).
2. Label the tube with the protocol, patient ID, patient initials, study visit, as well as the date of collection.
3. Record the date and time of collection on the Fresh Tumor Tissue Specimen Requisition (Appendix C in the Lab Manual).
4. Immediately submerge tissue in saline.

5. Keep specimen at room temperature.
6. Specimens collected in the late afternoon may be stored overnight at 4°C.
7. Transfer immediately to the Correlatives Studies Program at the Princess Margaret Cancer Centre.

9.2.5 Blood Collection

9.2.5.1 Collection of Blood in Sodium Heparin (*NaHep*) Tubes for Plasma and PBMC Processing

Blood collected in sodium heparin tubes should be processed locally into plasma and PBMCs. Sites that are unable process samples locally may ship samples ambient, day of collection, to the Correlative Studies Program at the Princess Margaret Cancer Centre (University Health Network), Monday to Wednesday Only. If samples are collected on a Thursday, Friday or before a holiday, sites will be responsible for processing the PBMC and plasma samples.

Patients will be requested to have 3 blood samples collected (sodium heparin) for exploratory analysis at different time points:

- at baseline before starting treatment (prior to day 1 cycle 1),
- during treatment before being dosed: at cycle 1 day 15 (week 2), and at day 1 of each following cycle.
- and at the time of progression.

For samples to be processed at UHN:

1. Label the tube with the protocol, patient ID, patient initials, and study visit, as well as the date of collection.
2. Collect 30 mL of whole blood in sodium heparin vacutainers (3 x 10 mL).
3. Samples must be kept at room temperature after collection.
4. Complete a PBMC & Plasma Specimen Requisition Form (Appendix C in the Lab Manual). This form should be included in the sample shipment.
5. Ship samples ambient, day of collection, to the Correlatives Studies Program at The Princess Margaret Cancer Centre, Monday – Wednesday only.

For samples to be processed locally:

1. Label the tube with the protocol, patient ID, patient initials, study visit, as well as the date of collection.
2. Collect 30 mL of whole blood in sodium heparin vacutainers (3 x 10 mL).
3. Samples must be kept at room temperature after collection.
4. Isolate PBMCs and Plasma as per Appendix E of the Lab Manual.
 - At Baseline only, one aliquot of PBMCs should be snap-frozen. The remaining aliquots will be cryopreserved. At all other visits, all cells will be cryopreserved.
5. Complete a PBMC & Plasma Specimen Requisition Form (Appendix C in the Lab Manual). This form should be included in the sample shipment.
6. Ship cryovials containing frozen plasma and PBMCs on dry ice to the Correlatives Studies Program at The Princess Margaret Cancer Centre.
7. Include a copy of the PBMC Processing Worksheet (Appendix E in the Lab Manual).

9.2.5.2 2mL EDTA Tube for CIMAC germline analysis

Germline blood for CIMAC analysis may be collected at baseline (preferred), or at any time. Every effort should be made to obtain EDTA whole blood from previously enrolled patients.

1. Label purple-top EDTA tubes according to the instructions in Section 9.3.1.
2. Collect 2 mL blood in EDTA tube(s) and gently invert 8-10 times to mix.
3. Maintain blood at ambient temperature during collection and transport.
4. Enter the appropriate information into the specimen tracking system (STS), see Section 9.3.
5. Ship on day of collection to the ETCTN Biorepository (whenever possible) according to instructions in Section 9.4.
6. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

9.3 Specimen Tracking System Overview and Enrollment Instructions (for samples being sent to ETCTN Biorepository only)

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
 - Institution and affiliate name
 - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in [Section 3](#)
- Additional Requirements:
 - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. If pathology reports are not available, please complete the Pathology Verification Form provided in [Appendix G](#). **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

9.3.1 Specimen Labeling

All Specimens being sent to the ETCTN Biorepository should be labeled as follows. If samples have been labeled per prior instructions, they should be re-labeled prior to transfer to the Biorepository. PBMC samples that have been received and processed at Princess Margaret Cancer Centre prior to protocol amendment 5 will be re-labelled by the Princess Margaret's Correlatives program prior to transferring to the ETCTN Biorepository for CIMAC assays.

9.3.1.1 Blood Specimen Labels (frozen plasma, frozen PBMCs, snap-frozen PBMC Cell Pellet, and EDTA whole blood)

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type
- Collection date

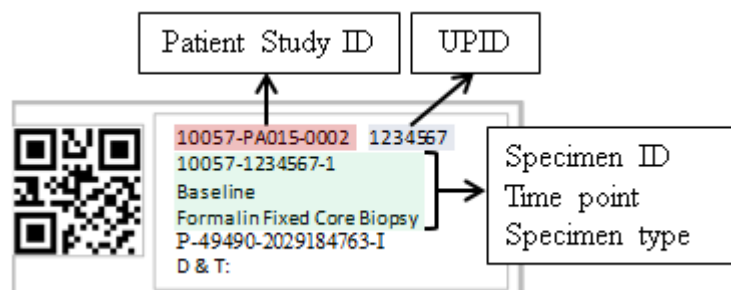
9.3.1.2 Tissue Specimen Labels (FFPE Blocks or Archival Slides)

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date and core #

9.3.1.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avrey label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

NOTE: The QR code label is currently under development at Theradex as of 05-Jul-2019; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.3.2 Overview of Process at Treating Site

9.3.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be set up with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

9.3.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 9.3.1.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen-specific pathology or related report (one per specimen). Uploaded reports should have PHI data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list; one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click “Send Email Alert” checkbox on the **Shipping Status** CRF to the email recipient.

Step 7: Ship the specimen(s).

9.4 Shipping Specimens from the Clinical Site to the ETCTN Biorepository

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not available, then the surgical and/or radiology report must be uploaded to the ETCTN specimen tracking system and included in the package, or the specimen will not be processed.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist. If pathology reports are not available, please complete the Pathology Verification Form provided in [Appendix G](#).

9.4.1 Specimen Shipping Kits (for specimens being sent to the ETCTN Biorepository only)

Sites are responsible for providing shipping materials. No kits will be provided.

9.4.2 Specimen Shipping Instructions

9.4.2.1 Shipping of FFPE Blocks or Slides

- Ship blocks and slides to the ETCTN Biorepository on Monday through Thursday by FedEx Priority Overnight.
- Include a cold pack when shipping on hot days and include extra insulation on cold days.
- Blocks should be placed in a special block holder, if possible. Slides must be packaged in plastic slide holders.
- Ship blocks and slides in a box or padded envelope with a copy of the corresponding pathology report (if available) and a shipping manifest from the Specimen Tracking System.

9.4.2.2 Shipping of Frozen Plasma, PBMCs, and Cell Pellets (from Princess Margaret Cancer Centre to the ETCTN Biorepository)

- Sites should ship specimens to the Princess Margaret Cancer Centre (refer to Section 9.5.2 and 9.5.3) for storage.
- At the time of sample analysis, frozen plasma, PBMCs and cell pellets will be batch shipped on dry ice from Princess Margaret/UHN to the ETCTN Biorepository by overnight courier.
- Frozen specimens may be shipped on Monday through Thursday.
- FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
- A shipping manifest from the Specimen Tracking System must be included with each shipment.
- Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment.

9.4.2.3 Shipping EDTA Tube for CIMAC germline analysis

- Fresh blood may be shipped on Monday through Friday. Please select “Saturday Delivery” when shipping fresh blood on a Friday.
- An external sample label should be fixed to the shipping container to alert the Biorepository of blood sample collection time and date (this helps to identify and prioritize received samples that have processing time requirements).
- Blood should be shipped ambient FedEx Priority Overnight to the biorepository where it is processed the day of receipt, ideally within 24 hours of collection.

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9.4.3 Shipping Address

Ship to the address below. Do not ship specimens the day before a USA holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
Ph: (614) 355-5823
FAX: (614) 722-2856

Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

9.4.4 Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

9.5 Shipping of Specimens from Clinical Site to Princess Margaret Cancer Centre

9.5.1 Refrigerated Fresh Tissue Shipping Procedures (non-UHN sites)

1. Place 1-2 refrigerated gel packs in a Styrofoam box.
2. Parafilm the top of the specimen container to seal. Insert the container in a biohazard bag. Remove all air from the biohazard bag and seal at the top.
3. Place the specimen requisition form in the outer pocket of the biohazard bag.
4. Wrap the bag containing the specimen with a refrigerated gel pack and place inside the Styrofoam box.
5. Add 1-2 refrigerated gel packs on top of the specimen.
6. In the summer months, add an extra frozen gel pack before closing the Styrofoam box.
7. Place the Styrofoam box inside a cardboard box.
8. Label the shipping container with appropriate labels and shipping addresses.
9. Ship package (Monday to Wednesday) to the Correlatives Studies Program at The Princess Margaret Cancer Centre.
10. Complete and email a copy of the Notification of Sample Shipment Form (Appendix D in the Lab Manual) on the day of shipment.

9.5.2 Shipping of Ambient Sodium Heparin Blood to UHN for Processing (non-UHN Sites)

1. Insert the filled tubes into the separate pockets of the absorbent sleeve.
2. Place the sleeve inside of the biohazard bag, remove all air from the biohazard bag and seal at the top.
3. Place the completed PBMC & Plasma Specimen Requisition (Appendix C in the Lab Manual) in the outer pocket of the biohazard bag.
4. Wrap the biohazard bag containing the filled blood tubes with an ambient gel pack. Do not freeze or refrigerate the gel packs.
5. Place packaged tubes inside the ambient shipping box.
6. Label the shipping container with appropriate labels and shipping addresses.
7. Ship package ambient, day of collection, to the Correlative Studies Program at The Princess Margaret Cancer Centre (Monday to Wednesday only).
8. Complete and email a copy of the Notification of Sample Shipment form (Appendix D in the Lab Manual) on the day of shipment.

9.5.3 Shipping of Frozen Plasma, PBMCs, and Snap-Frozen Cell Pellet to UHN

1. Take the shipping box and add a one-inch layer of dry ice to the bottom of the Styrofoam insert.
2. Remove frozen samples from liquid nitrogen. Place samples in a sealed biohazard bag.
3. Place the completed PBMC & Plasma Specimen Requisition (Appendix C in the Lab Manual) in the outer pocket of the biohazard bag.
4. Include a copy of the PBMC Processing Worksheet (Appendix E in the Lab Manual) with sample shipment.
5. Place the sealed biohazard bag(s) containing the samples at the bottom of the Styrofoam shipping box.
6. Surround and cover the box(es) containing the samples with as much dry ice as possible, filling the shipping box. The shipping box should be completely full.
7. Label the shipping container with appropriate labels and shipping addresses.
8. Ship frozen on dry ice to the Correlatives Studies Program at The Princess Margaret Cancer Centre (Monday to Wednesday only).
9. Ensure that the shipping box is large enough to accommodate a generous amount of dry ice to maintain the temperature of the sample(s) for the length of the transient time plus an additional 24 hours. Failure to do so can result in thawing of the specimen(s), which will render it unusable for the study purposes.
10. Complete and email a copy of the Notification of Sample Shipment form (Appendix D in the Lab Manual) on the day of shipment.

9.5.4 Shipping Address

Ship samples to the address below. Please ensure that shipments are not scheduled to arrive on holidays observed in Ontario, Canada (please see Lab Manual for details):

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

FedEx is preferred.

Additional instructions for shipping within Canada and international shipping to Canada can be found in the Lab Manual.

9.5.5 Contact Information for Assistance

For laboratory questions, please call:

Vanessa Speers
Program Manager
Correlative Studies Program
Tel: (416) 946-4501 ext. 2562
Fax: (416) 946-2048
Email: vanessa.speers@uhn.ca

For shipping questions, please call:

Correlative Studies Office
Tel: (416) 946-4501 ext. 5047
Fax: (416) 946-4431
Email: CCRUCorrelativestudies@uhn.ca

9.6 Biomarker Plan

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	PD-L1	IHC CLIA: Y	Integrated Assess the impact of PD-L1 expression within tumor micro-environment	Archival Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	M	CIMAC (Mt. Sinai – Dr. Aktruk)
2	Tumor-Infiltrating Lymphocytes (TILs) & Vascularization	mIHC CLIA: N	Integrated 1) Assess TILs as a predictive biomarker	Archival Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	M	CIMAC (Mt. Sinai – Dr. Aktruk)
3	CD31	IHC CLIA: N	Exploratory Assess anti-angiogenic effects of cabozantinib	Archival Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	M	CIMAC (Mt. Sinai)

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	WES	NGS CLIA: N	Exploratory 1) Tumor somatic mutation burden (TMB) estimation; 2) Dynamics of TMB upon treatment	Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	M	CIMAC
5	RNAseq	RNAseq CLIA: N	Exploratory 1) Detect presence of MET mutation or its amplification in baseline biopsy; 2) Assess evolution of MET mutations/amplification following disease progression at RNA level; 3) Evaluate the genome for evidence of clonal evolution among longitudinal samples; 4) Compare MET expression and genotypic patterns among responders and non-responders	Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	M/O ^{i, ii}	CIMAC
6	TCRseq	Adaptive CLIA: N	Exploratory TCR clonality changes upon treatment	Biopsy - FFPE	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	O (if adequate tissue is available)	Adaptive Biotechnologies working with CIMAC
7	Tumor Immune Pheno-typing	CytoF CLIA: N	Exploratory Quantifying population frequencies of major immune subsets	Biopsy – Fresh in media	Baseline ⁱⁱⁱ Progression ⁱ Cross-over ⁱⁱ	O (if adequate tissue is available)	PMH (Dr. Ohashi)
8	MMR Status	IHC CLIA: N	Exploratory Determine MMR status of enrolled patients	Archival	Archival	M/O ^{i, ii}	PMH (Pathology Department)

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
9	MMR Status	IHC CLIA: N	Exploratory Determine MMR status of enrolled patients	Biopsy – FFPE 5 slides if available	Baseline ⁱⁱⁱ	M/O ^{i, ii}	PMH (Pathology Department)
10	Pilot Study ^{viii} Spatial Transcriptomics	GeoMX ^{vi} (CLIA:N)	Exploratory 1) Determine spatial distribution of MET expression and MET-induced gene signature 2) Assess spatial distribution of immune exhaustion markers 3) Compare dynamics of spatial gene expression changes among responders and non-responders	Biopsy - FFPE	Baseline ⁱⁱⁱ Progression Cross-over ⁱⁱ	As available	CIMAC (Mt. Sinai – Dr. Gnjjatic)
11	Pilot Study ^{viii} Spatial Transcriptomics	Visium ^{vii} (CLIA:N)	Exploratory 1) Determine spatial distribution of MET expression and MET-induced gene signature 2) Assess spatial distribution of immune exhaustion markers 3) Compare dynamics of spatial gene expression changes among responders and non-responders	Biopsy - FFPE	Baseline ⁱⁱⁱ Progression Cross-over ⁱⁱ	As available	CIMAC (Mt. Sinai – Dr. Gnjjatic)
Blood-based Biomarkers							
1	Grand Serology	ELISA CLIA: N	Exploratory Antibody profiling, to measure changes in known tumor antigen-specific antibody responses	Plasma	C1D1 pre-dose C2D1 C4D1 Progression	M	CIMAC (Mt. Sinai – Dr. Gnjjatic)

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	Cytokine Profiling	O-link CLIA: N	Exploratory Quantification of cytokine levels	Plasma	C1D1 pre-dose C2D1 C4D1 Progression	M	CIMAC (Mt. Sinai – Dr. Kim-Schulze)
3	Circulating Immune Cells	CyTOF CLIA: N	Exploratory Estimate population frequencies of major immune subsets and quantify markers of immune activation of suppression	PBMC	C1D1 pre-dose C2D1 C4D1 Progression	M	CIMAC (Mt. Sinai – Dr. Rahman)
4	Chemokine/ Cytokine Profiling	Luminex CLIA: N	Exploratory Quantification of chemokines / cytokine levels	Plasma	C1D1 pre-dose C2D1 C4D1 Progression ^{iv}	M	PMH (Dr. Butler/ Ohashi)
5	Circulating Immune Cells	CyTOF / Flow	Exploratory Estimate population frequencies of major immune subsets and quantify markers of immune activation or suppression	PBMC	C1D1 pre-dose C2D1 C4D1 Progression ^{iv}	M	PMH (Dr. Butler/ Ohashi)
6	Germline analysis	DNA sequencing CLIA: No	Exploratory Control to exclude germline variants for accurate data interpretation of tumor DNA sequencing	Whole blood	Baseline ^v	M ^v	CIMAC
7	TCRseq	Adaptive Immunosequencing CLIA: N	Exploratory TCR clonality changes upon treatment	DNA from blood/ PBMC	C1D1 pre-dose (Baseline) C1D15 C2D1 C3D1 C4D1 Crossover Progression	M	Adaptive Biotechnologies working with CIMAC

ⁱ At time of progression, all patients will be consented to have an optional tumor biopsy.

ⁱⁱ Patients enrolled in Arm B can be crossed-over to Arm C at time of progression. A mandatory biopsy will be required for any patients choosing to cross-over to this exploratory cohort.

- iii Baseline tissue is given priority although if adequate tissue supply is unavailable, archival tissue will be used.
- iv Priority will be given to CIMAC for samples collected at C1D1 pre-dose, C2D1, C4D1, and Progression. If there are more specimens available, all timepoints will also be analyzed by PMH.
- v Germline blood for CIMAC analysis may be collected at baseline (preferred), or at any time. Every effort should be made to obtain EDTA whole blood from previously enrolled patients. In cases where this is not possible to obtain, the snap frozen PBMC cell pellet, or adjacent normal tissue from baseline biopsy or archival tissue, may be used for CIMAC analysis.
- vi GeoMX will be performed on a subset of patients that will include seven MSI-subjects and matched controls, plus a subset of responders and non-responders.
- vii The Visium assay requires that tissue blocks be sent to the Mount Sinai CIMAC. This assay is contingent on the biobank sending tissue blocks to Mount Sinai.
- viii Assay will be performed as a pilot to assess the application of spatial transcriptomics using FFPE tissue.

9.7 Integrated Correlative Studies

9.7.1 PD-L1 expression on biopsy and archival tissue.

Hypothesis: Expression of PD-L1 in endometrial cancer may correlate with response to immune checkpoint inhibitors.

To date, no definitive data are available to confirm the role of PD-L1 expression as predictive biomarker of response. For this purpose, PD-L1 expression will be assessed on baseline biopsy and correlated with patient outcome. Archival tissue will also be assessed if adequate baseline tissue is unavailable.

PD-L1 expression will be detected using immunohistochemistry (IHC) per a CIMAC-approved assay. The ETCTN Biorepository will store specimens and distribute to the designated CIMAC laboratory. Instructions on how to distribute tissue specimens to the downstream CIMAC laboratories are to be determined.

9.7.1.1 Site(s) Performing Correlative Study

PD-L1 will be performed through the CIMAC at the Icahn School of Medicine at Mount Sinai under Dr. Guary Aktruk.

9.7.2 TILs and Vascularization analysis by mIHC on biopsy and archival tissue

Hypothesis: Tumor microenvironment plays a relevant role in favoring sensitivity or resistance to a specific antineoplastic treatment, representing a potential predictive biomarker. Presence and distribution of regulatory and cytotoxic T cells may favor resistance or sensitivity to treatment, respectively. Combination of antiangiogenic agents and immune check-point inhibitors may favor improvement of effector T cell function and reduction in T regs^{76,77}. In addition, we seek to evaluate the clinical relevance of angiogenic markers in endometrial cancer, and investigate the therapeutic efficacy

of targeting of receptor tyrosine kinases (i.e. MET, VEGFR2, FLT3, c-KIT, and RET) using cabozantinib in combination with nivolumab.

The TILs and vascularization mIHC assays will be performed in a CIMAC laboratory using a CIMAC-approved assay. The ETCTN Biorepository will store specimens and distribute to the designated CIMAC laboratory. Instructions on how to distribute tissue specimens to the downstream CIMAC laboratories are to be determined.

Results will be correlated with patient outcome to define potential predictive biomarkers. If the patient will agree to have the optional biopsy at the time of progression, we will assess changes in immune cell infiltrates, and angiogenic markers, following treatment with nivolumab or nivolumab plus XL184.

9.7.2.1 Site(s) Performing Correlative Study

Multiplex IHC assays will be performed through the CIMAC at the Icahn School of Medicine at Mount Sinai under Dr. Guray Aktruk.

9.8 Exploratory/Ancillary Correlative Studies

9.8.1 MMR status assessed by IHC on baseline biopsy and archival tissue

Hypothesis: patients with MMR deficient endometrial cancer have higher response rate to immune checkpoint inhibitors.

MSI can be assessed through IHC with good accuracy, assessing 4 MMR proteins: MLH1, PMS2, MSH2 and MSH6^{6,80}.

Endometrial cancer characterized by MSI have high neo-antigens expression, are more immunogenic than MSS tumors and have higher level of TILs⁴.

No data are available on evolution of MSI and MMR status and immune microenvironment status in serial tumor samples in patients with different histological subtypes of endometrial cancer. We will explore the presence of differences in MMR status between archival tissue and baseline biopsy and correlate this with outcome.

9.8.1.1 Site(s) Performing Correlative Study

Analysis of MMR status from the archival tissue will be reviewed and centralized at Pathology Department at the Princess Margaret Cancer Centre. If available after CIMAC analysis, an additional 5 slides from the baseline biopsy tissue will be sent to the Pathology Department at the Princess Margaret Cancer Centre for analysis. Specimens will be stored in the ETCTN Biorepository then distributed to the Princess Margaret Cancer Centre.

9.8.2 Whole Exome Sequencing (WES)

According to TCGA classification, endometrial cancers can be classified in four different groups based on somatic nucleotide substitution, copy number variations and MSI³.

Assessment of somatic genomic mutations may help to molecularly characterize endometrial cancer and define their correlation with patient outcome. Identification of potential molecular predictive biomarkers may help to better select patients more likely to benefit from nivolumab or combination of nivolumab and XL184.

We will assess the presence of somatic mutations using next generation sequencing (NGS) on baseline tissue and correlate this with outcome to identify potential biomarkers of response. We will also define clonal evolution of endometrial cancer comparing the burden and type of somatic mutations at baseline and progression.

9.8.2.1 Site(s) Performing Correlative Study

Analysis of somatic mutations will be performed through CIMAC. The ETCTN Biorepository will store specimens and distribute to the designated CIMAC laboratory. Instructions on how to distribute tissue specimens to the downstream CIMAC laboratories are to be determined.

9.8.3 MET Mutation and Protein Expression

Hyperactivation of HGF/MET pathway is present in 60% of endometrial cancer and is relevant in endometrioid and serous histology and targeting this tyrosine kinase receptor inhibits both angiogenic and mitotic pathways^{14,52}.

In this study, we will assess the presence of MET mutation or its amplification on biopsy specimens by RNAseq. This will then be correlated with patient outcome to explore their role as predictive biomarkers. MET expression and mutation status will also be compared with potential aberrations found in archival tissue, to explore the evolution of MET mutations/amplification following disease progression at the RNA level.

9.8.3.1 Site(s) Performing Correlative Study

MET mutation will be assessed using RNAseq performed through CIMAC. The ETCTN Biorepository will store specimens and distribute to the designated CIMAC laboratory. Instructions on how to distribute tissue specimens to the downstream CIMAC laboratories are to be determined.

9.8.4 T cell Receptor Sequencing (TCRseq)

Hypothesis: The TCR repertoire may represent a predictive factor for response to mono- (nivolumab) or combination (nivolumab + cabozantinib) therapy.

We will assess changes in the TCR repertoire during treatment using TCRseq on biopsy specimens and in PBMCs. This will then be correlated with patient outcome to explore their role as predictive biomarkers.

9.8.4.1 Site(s) Performing Correlative Study

Samples may be transferred from Princess Margaret Centre to EET Biobank as needed and appropriate for EET Biobank to process for sending to CIMAC. TCRseq in PBMCs and Tumor will be performed through Adaptive Biotechnologies working with the CIMACs. The ETCTN Biorepository will store specimens and distribute to the designated CIMAC laboratory or the associated lab Adaptive Biotechnologies. Instructions on how to distribute tissue specimens to the downstream CIMAC laboratories are to be determined.

9.8.5 Immune markers analysis on biopsy specimens

Hypothesis: Tumor microenvironment may represent a predictive factor for response to immune checkpoint inhibitor and antiangiogenic agents^{4,59}.

Fresh biopsy samples will be analyzed using flow cytometry and/or mass cytometry (CyTOF) at the Translational Immunotherapy Laboratory – Princess Margaret Cancer Centre (Dr. Ohashi) in order to assess specific immune populations. Analysis will include effector T cells, B cells, NK cells, and myeloid subsets, as well as the activation/exhaust.

After adequate amount of tumor tissue will be reserved for IHC (integrated biomarkers) the remaining tissue will be digested into a single cell suspension using an enzymatic and mechanical dissociation method (Gentle MACS, Miltenyi Biotech) that preserves cell viability and surface epitopes. Cells will be viably frozen and stored in liquid nitrogen until all samples can be run in batch. This will ensure that genomic and flow cytometry/CyTOF-based immune profiling is cost-efficient and it will reduce day-to-day technical variability.

Flow cytometry/CyTOF panels will include markers such as CD45, CD45RA, CD45RO (immune cells); CD3, CD4, CD8, FOXP3 (T-cell subsets), TCRgd (gamma-delta T-cells); NKp46 (NK cells), CD11c, CD14, CD16, HLA-DR (myeloid cells), PD-L1, PD-1, TIGIT, CTLA-4, 4-1BB, CD31, CD133 (immune checkpoint); Fas, Granzyme B (cytotoxicity); CD27, CD28 (T-cell co-stimulation); CD25, CD127, Helios, ICOS, CD39 (Treg markers); CD103, CD69, CXCR3 (T-cell infiltration); and Ki67 (cell proliferation).

Results from this analysis will be correlate with patient outcome to explore possible biomarkers of response.

9.8.5.1 Site(s) Performing Correlative Study

Immune phenotyping profiling on tumor tissue will be performed at the Translational Immunotherapy Laboratory- Princess Margaret Cancer Centre (Dr.Ohashi).

9.8.6 Grand Serology

Hypothesis: Antibody responses may correlate with patient outcomes (PFS, ORR, OS)

Antibody body profiling can be used to analyze the humoral immune response in peripheral blood. In this study, antibody titers will be assessed in plasma samples by enzyme-linked immunosorbent assay (ELISA)/Grand Serology. Plasma will be obtained from sodium heparin tubes (see Section 9.2.5 for collection instructions). Antibodies will be measured at selected time points (pre-dose C1D1, C2D1, C4D1 and at progression).

9.8.6.1 Site(s) Performing Correlative Study

Grand serology will be performed by the CIMAC at the Icahn School of Medicine at Mount Sinai under Dr. Sacha Gnjatich. Specimens will be shipped from sites to the Princess Margaret Cancer Centre (see Section 9.5). At the time of analysis, plasma samples will be batch shipped from Princess Margaret to the ETCTN Biorepository, then distributed to the designated CIMAC laboratory.

9.8.7 Cytokine Profiling

Hypothesis: Cytokine responses may correlate with patient outcomes (PFS, ORR, OS)

The humoral immune response can be characterized by quantifying changes in soluble analytes, such as cytokines. In this study, cytokine levels will be determined using the O-link platform; performed through the CIMAC at the Icahn School of Medicine at Mount Sinai. Plasma will be obtained from sodium heparin tubes (see Section 9.2.5 for collection instructions). Cytokines will be measured at selected time points (pre-dose C1D1, C2D1, C4D1 and at Progression).

At all other time points, multiplex platforms, such as the Luminex platform, may also be used to measure chemokines/cytokines involved in pro-inflammatory innate responses such as $\text{INF}\alpha$ through the Translational Immunotherapy Laboratory at Princess Margaret Cancer Centre (Dr. Butler/Ohashi). Priority will be given to CIMAC samples collected at C1D1 pre-dose, C2D1, C4D1, and Progression. If sufficient plasma is available, these time points will also be analyzed at PMH.

9.8.7.1 Site(s) Performing Correlative Study

Cytokine profiling using the O-link assay will be performed at the Icahn School of Medicine at Mount Sinai under Dr. Kim-Schulze at select time points.

If adequate samples are available, chemokines/cytokines may also be measured using multiplex platforms, such as the Luminex platform, at the Princess Margaret Cancer Centre - Translational Immunotherapy Laboratory (Dr. Butler/Ohashi).

Specimens will be shipped from sites to the Princess Margaret Cancer Centre (see Section 9.5). At the time of analysis, plasma samples will be batch shipped from Princess Margaret to the ETCTN Biorepository, then distributed to the designated CIMAC laboratory.

9.8.8 Immune markers assessed by flow cytometry and/or CyTOF on peripheral blood

Hypothesis: Treatment with nivolumab may induce change in peripheral immune landscape. The addition of an antiangiogenic agent to the immune checkpoint inhibitor nivolumab may reduce the

cancer-related immune suppressive microenvironment, favoring increase activity of immune therapy^{76,77}.

An exploratory analysis of peripheral blood will be performed to phenotypically characterize cellular subsets such as effector lymphocytes, regulatory T cell and myeloid subsets. Analysis will be performed using flow cytometry and/or CyTOF (as sample material allows). Assays will be conducted through both the CIMAC at the Icahn School of Medicine at Mount Sinai, and the Princess Margaret Cancer Centre (Translational Immunotherapy Laboratory; Dr. Butler/Ohashi). Panels will include markers such as CD45RA, CD45RO (immune cells); CD3, CD4, CD8, FOXP3 (T-cell subsets), TCRgd (gamma-delta T-cells); NKp46 (NK cells), CD19 (B cells), CD11c, CD14, CD16, HLA-DR (myeloid cells); PD-L1, PD-1, TIGIT, CTLA-4, 4-1BB, CD31, CD133 (immune checkpoint); Fas, Granzyme B (cytotoxicity); CD27, CD28 (T-cell co-stimulation); CD25, CD127, Helios, ICOS, CD39 (Treg markers); CD103, CD69, CXCR3 (T-cell infiltration); and Ki67 (cell proliferation).

PBMCs will be obtained from sodium heparin tubes (see Section 9.2.5 for collection instructions). Immune subsets will be measured at selected time points by CIMAC (pre-dose C1D1, C2D1, C4D1 and at Progression). At all other time points, testing will be performed through the Translational Immunotherapy Laboratory at Princess Margaret Cancer Centre (Dr. Butler/Ohashi). Priority will be given to CIMAC samples collected at pre-dose C1D1, C2D1, C4D1 and Progression. If sufficient cells are available, these time points will also be analyzed at Princess Margaret.

In our study, we will assess the immune markers landscape at baseline, during treatment and correlate with outcome and explore the differences between the two treatment arms (immune checkpoint alone versus immune checkpoint in combination with the antiangiogenic agent, XL184). In other tumor types, preliminary data have shown that antiangiogenic agents might have a role in reversing the immune-suppressive microenvironment, increasing the activity of effector T cells and reducing regulatory T cells, supporting the rationale to combine immune therapy with antiangiogenic agents^{76,77}. We will further explore this in our population of patients with different histological subtypes of endometrial cancer.

9.8.8.1 Site(s) Performing Correlative Study

Immune markers on peripheral blood will be assessed at the Icahn School of Medicine at Mount Sinai under Dr. Rahman, at select time points.

If adequate samples are available, assays will also be performed at the Translational Immunotherapy Laboratory at Princess Margaret Cancer Centre (Dr. Butler/Ohashi).

Specimens will be shipped from sites to the Princess Margaret Cancer Centre (see Section 9.5). At the time of analysis, PBMC samples will be batch shipped from Princess Margaret to the ETCTN Biorepository, then distributed to the designated CIMAC laboratory.

9.8.9 2mL EDTA Tube for CIMAC germline analysis

Whole blood will be collected as a control for WES to exclude germline variants for accurate data interpretation of tumor DNA sequencing.

The ETCTN Biorepository will prepare 0.5 mL aliquots of whole blood upon receipt. Aliquots of whole blood will be stored in a -80°C freezer until distribution for analysis.

Instructions on how to thaw, aliquot, and distribute blood specimens to the downstream CIMAC laboratories will be added at a later time.

9.8.9.1 Site(s) Performing Correlative Study

DNA sequencing will be performed through CIMAC. Specimens will be stored at the ETCTN Biorepository then distributed to the appropriate CIMAC laboratory.

9.8.10 GeoMX and Visium (spatial transcriptomics)

Performance of the GeoMX and Visium spatial transcriptomic assays by CIMAC will require that the EET Biobank (formerly the ETCTN Biorepository) send the FFPE block(s) to the CIMAC (Mt Sinai CIMAC). A sample request will be sent to the EET Biobank specifying which blocks should be sent to CIMAC. The CIMAC will work with EET Biobank to follow the requirements for return of the FFPE blocks to the EET Biobank.

GeoMX and Visium (spatial transcriptomics) will be used to:

1. Evaluate spatial distribution of prognostic biomarkers defined in RNAseq assay. Uniform versus clonal distribution pattern of expression will inform mechanism of tumor evolution following disease progression.
2. Identify immune subsets, exhaustion and activation status. Evaluate spatial distribution of immune markers and associated gene expression. Correlate patterns with therapy response and resistance.
3. Compare performance of two methods.

The goal is to compare the strengths, weaknesses, and relevance of both techniques, as they are the current leading commercially available methodologies for spatial transcriptomics, and start linking data to clinical outcome. The rationale for using these precious samples is not only technological, but also to take advantage of the well-defined and frequent clinical responses observed in patients from this study, with the goal of linking spatial information in a representative subset of responders and non-responders to other Tier 1 assay data generated on the entire cohort. The data richness expected from this study will be a critical component of any manuscript, and is most justified for this trial due to a balanced response rate. Two types of analyses will be performed: concordance of number of expressed probes detected by both technologies and comparison of normalized gene expression.

To justify the significance of 10104 trial samples for this technology comparison project, we envision several biological reasons. The trial is composed from MSIH and MSS samples, which have been shown to have extremely different spatial expression profiles (PMID: 34450029). That means we have high

likelihood to estimate gene expression derived from (1) tissue-specific, (2) cancer-specific, (3) immune-infiltrate, (4) inflamed, (5) immunologically-cold spatial domains. This biological variability of spatial domains will add another layer of robustness to our technology-comparison strategy.

GeoMX and Visium will be performed on a subset of patients that will include seven MSI-subjects and matched controls, plus a subset of responders and non-responders.

Further details about the proposed spatial transcriptomics analyses and analysis plan are provided in the “Proposal Intake Form for Correlative Studies Using the CIMAC-CIDC Network”.

9.8.10.1 Site(s) Performing Correlative Study

The spatial transcriptomics assays (GeoMX and Visium) will be performed through Mt. Sinai CIMAC.

Table 9.2 Summary of Specimen Analysis

Time Point	Specimen	Lab
Tissue-based Analysis		
Archival	FFPE	PMH
Baseline	FFPE	CIMAC
	Biopsy – Fresh in media	PMH
Progression	FFPE	CIMAC
	Biopsy – Fresh in media	PMH
Cross-Over	FFPE	CIMAC
	Biopsy – Fresh in media	PMH
Blood-based Analysis		
C1D1 pre-dose	Plasma & PBMC	CIMAC ¹
C1D15	Plasma & PBMC	PMH
C2D1	Plasma & PBMC	CIMAC ¹
C3D1	Plasma & PBMC	PMH
C4D1	Plasma & PBMC	CIMAC ¹
Day 1 of each subsequent cycle	Plasma & PBMC	PMH
Progression	Plasma & PBMC	CIMAC ¹
Germline blood	Whole blood	CIMAC
¹ Priority will be given to CIMAC so that at least one aliquot of cryopreserved PBMC will be transferred to CIMAC for analysis. The remaining aliquots will be analyzed by PMH, if sufficient samples remain.		

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 10 days prior to start of protocol therapy, unless otherwise indicated. Scans, and biopsy must be done ≤ 28 and ≥ 7 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.

	Pre-study	Cycle 1 Day 1 (+/- 2 days)	Cycle 1 Day 15 (+/- 2 days)	Cycle 2,3,4 Day 1 (+/- 2 days)	Cycle 2,3,4 Day 15 (+/- 2 days)	Cycle 5+ Day 1 (+/- 2 days)	30-37 Day Safety Follow-up	Long-term follow up
XL184(Cabozantinib)		A	A	A	A	A		
Nivolumab		B	B	B	B	B		
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X	Performed throughout						
Physical exam	X	X	X	X	X	X	X	
Vital signs (BP ^e , HR, O2 Sat, Temp)	X	X	X	X	X	X	X	
Height	X							
Weight	X	X		X		X	X	
Performance status	X	X		X		X	X	
CBC w/diff, plts	X	X	X	X	X	X	X	
Serum chemistry ^a	X	X ^d	X	X	X	X	X	
CK, Troponin	X	X ^d	X	X	X	X		
PT, PTT	X							
TSH, T3, T4, ACTH, cortisol	X	X ^d		X		X	X	
Urinalysis, UPCR	X	X ^d		X		X	X	
ECG	X	X ^{d, f}	X	X ^f	X	X	X ^f	
Adverse event evaluation		Performed throughout						
Radiologic evaluation	X	Radiologic evaluation should be performed every 8 weeks (+/- 1 week) regardless of dosing holds						
Tumor measurements	X	Tumor measurements should be performed every 8 weeks (+/- 1 week) regardless of dosing holds. Documentation must be provided for patients removed from treatment for objective disease progression						
B-HCG ^b	X							
Tumor biopsy ^h	X						X ^g	
Archival tissue	X							
Research blood samples		X	X	X ⁱ		X ⁱ	X	
Blood for germline analysis		X ⁱ						
Patient status								X ^c

A: XL184(Cabozantinib) is administered continuously and orally on a daily basis, in cycle of 28 days

B: Nivolumab is administered via IV on Day 1 and 15, every 28 days, cycle 1-4. From cycle 5 nivolumab should be administered on Day 1 every 28 days.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, amylase, lipase.

b: Serum pregnancy test for women of childbearing potential only.

c: Survival follow-up is to be conducted every 12 weeks (+/- 2 weeks) via phone, clinic visit, or from health records.

d: Does not need to be repeated on C1D1 if screening assessment performed within 7 days prior to that date

e: Blood pressure to be measured by the patient on a daily basis for the first 28 days (recorded on the diary card); it is the physician's discretion if further monitoring is required.

f: Triplicate ECG if required as defined in section 3.2.22 and if at any time on study there is an increase in QTcF interval to an absolute value > 500 msec; two additional ECGs should be performed within 30 minutes after the initial ECG with intervals no less than 3 minutes apart (see section 6.1).

g: An optional tumor biopsy may be collected at the time of progression from consenting patients. Patients who progress on arm B (single agent nivolumab) who wish to cross over to XL184 (cabozantinib) and nivolumab combination are required provide this biopsy before starting the combination treatment.

h: Biopsy to be performed ≤ 28 and ≥ 7 days before treatment starting. Biopsy will be performed only if deemed safe. If risk of perforation or fistulization is present biopsy will be omitted.

i: Research blood samples to be taken at baseline before starting treatment (prior to day 1 cycle 1), during treatment before being dosed: at cycle 1 day 15 (week 2), at day 1 of each following cycle, and at the time of progression.

j: Germline blood for CIMAC analysis may be collected at baseline (preferred), or at any time. Every effort should be made to obtain EDTA whole blood from previously enrolled patients. In cases where this is not possible to obtain, the snap frozen PBMC cell pellet, or adjacent normal tissue from baseline biopsy or archival tissue, may be used for CIMAC analysis.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks regardless of dose delay.

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 nivolumab with or without 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 (≥ 2 cm) by chest x-ray or as ≥ 10 mm (≥ 1 cm) 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 can be considered as measurable disease, and used as a target lesion if applicable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] 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 (≥ 1 cm) 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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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.

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.

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 (<1 cm).

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 (0.5 cm). (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 if applicable. Note that 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 [<1 cm] 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
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> 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 “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>			

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
<p>* ‘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</p>		

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)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Overall Survival (OS)

Overall survival (OS) is defined as the time from start of treatment to time of death.

11.1.8 Overall Response Rate (ORR)

Overall Response Rate is defined as the number of patients achieving PR or CR out of all patients treated.

12. STUDY OVERSIGHT AND 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 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For a Phase 2 study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctscontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (<http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models>). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

A phase 2 open-label randomized design will be used to assess efficacy and safety between patients receiving combination of nivolumab and XL184 (Arm A) and patients receiving nivolumab alone (Arm B). Patients with recurrent, relapsed or metastatic endometrial cancer progressed after at least one line of platinum based chemotherapy will be randomized in a 2:1 ratio. All patients with endometrial carcinoma are eligible, regardless of histological subtype.

An exploratory cohort (arm C) will enroll:
- Patients with endometrial carcinosarcoma;

- Patients that will cross-over from arm B after progression to single agent nivolumab;
- Patients that have been previously treated with anti PD-1, PD-L1 and PD-L2.

Patients enrolled in arm C will receive combination of cabozantinib and nivolumab and will not be part of the statistical analysis for the primary endpoint, but safety data from arm C will be included in the evaluation of combination treatment safety.

Primary Objectives

- To evaluate the clinical anti-tumor activity of XL184 and nivolumab based on progression free survival (PFS) in patients with advanced, recurrent or metastatic endometrial cancer previously treated with at least one line of platinum based chemotherapy compared to patients receiving nivolumab alone.

Secondary Objectives

- To evaluate the efficacy of XL184 and nivolumab in terms of overall response rate (ORR) compared to nivolumab alone.
- To evaluate overall survival (OS) of patients receiving XL184 and nivolumab compared to patients receiving nivolumab alone.
- To evaluate the safety of XL184 and nivolumab combination in patients with advanced, recurrent or metastatic endometrial cancer.
- To evaluate correlation between PD-L1 expression, CD3, CD4 and CD8 infiltrates and outcome (PFS, ORR, OS).
- To compare PD-L1 expression, CD3, CD4 and CD8 infiltrates in the primary tumor (archival tissue) and in the tissue from baseline biopsy.
- To assess activity (PFS, ORR and OS) of nivolumab alone or in combination with XL184 according to MSI/MMR status.

Exploratory Objectives

- To assess activity (PFS, ORR and OS) of XL184 and nivolumab in patients progressed after previous exposure to anti PD-1, PD-L1 or PD-L2 agents or after receiving single agent nivolumab, and in patients with diagnosis of Carcinosarcoma (arm C).
- To compare MS and MMR status, in the primary tumor (archival tissue) and in the tissue from baseline biopsy.
- To assess the genomic and immune-markers landscape at baseline on tumor tissue and changes in immune landscape in peripheral blood during treatment and correlate with outcome

All patients who receive at least one dose of nivolumab or nivolumab and XL184XL184 will be assessed for safety. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0.

Once the first 6 patients receiving combination of cabozantinib and nivolumab (including arm A and Carcinosarcoma cohort from arm C) have each completed one cycle of treatment, a preliminary safety assessment is planned (see section 5.3). Further accrual to the study will be put on hold until completion of the preliminary safety assessment.

13.2 Planned Futility Analysis

When 24 PFS events (50% information time) have been recorded, recruitment to the study will be put on hold for a planned futility analysis. If PFS in patients treated on Arm A (nivolumab and XL184) is seen to be inferior to patients treated on Arm B (nivolumab), the combination treatment will be declared ineffective, and the study will be terminated (reference Wieand S., Schroeder G., O'Fallon JR Stopping when the experimental regimen does not appear to help. Stat Med 1994; 13: 1453-58).

13.3 Sample Size/Accrual Rate

Fifty-four patients (36 in arm A and 18 in arm B) with advanced, recurrent or metastatic epithelial endometrial cancer should be enrolled to observe 48 PFS events total and achieve, with a one-sided log rank test, 80% power at a 0.10 significance level to detect a hazard ratio of 0.50 when the control group median survival time is 3 months (median PFS for the experimental group: H0: 3 months, H1: 6 months). The study is estimated to last for 24 months, of which subject accrual (entry) occurs in the first 18 months. 5% loss of follow up is considered for this sample size estimation.

The primary objective is the PFS between arm A (nivolumab plus cabozantinib) versus arm B (nivolumab alone); based on an intent to treat (ITT) analysis. If 48 PFS events among 54 patients will be not met, a maximum of 6 additional patients can be enrolled. When treatment is discontinued before first radiological assessment, patients will be censored and included in the primary analysis.

All patients will be evaluable for safety.

In the exploratory cohort (arm C), combination of cabozantinib and nivolumab will be considered for further investigation if at least 1 partial response and 1 stable disease lasting at least 16 weeks will be observed. Expected accrual for arm C is up to 20 patients who are post-PDL-1, and 10 patients with carcinosarcoma.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown / Not Reported Ethnicity			
	Female	Male	Unknown / Not Reported	Female	Male	Unknown / Not Reported	Female	Male	Unknown / Not Reported	
American Indian/ Alaska Native	3	0	0		0	0	0	0	0	3
Asian	19	0	0	0	0	0	0	0	0	19
Native Hawaiian or Other Pacific Islander	1	0	0	0	0	0	0	0	0	1
Black or African American	17	0	0	0	0	0	0	0	0	17
White	24	0	0	9	0	0	0	0	0	33
More Than One Race	11	0	0	0	0	0	0	0	0	11
Unknown or Not Reported		0	0	0	0	0	0	0	0	
Total	75	0	0	9	0	0	0	0	0	84

Expiration Date: 10/31/2018

OMB No. 0925-0001/0002

DOMESTIC PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	2	0	0	0	2
Asian	9	0	0	0	9
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	9	0	0	0	9
White	13	0	6	0	19
More Than One Race	5	0	0	0	5
Total	39	0	6	0	45

INTERNATIONAL (INCLUDING CANADA) PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	10	0	0	0	10
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	8	0	0	0	8
White	11	0	3	0	14
More Than One Race	6	0	0	0	6
Total	36	0	3	0	39

13.4 Stratification Factors

Patients will be stratified according MS/MMR status defined as per local guidelines.

13.5 Analysis of Secondary Endpoints

Summary statistics, such as mean, median, counts and proportion, will be used to summarize the patients. Survival estimates will be computed using the Kaplan-Meier method. Potential association between variables will be measured using Pearson correlation coefficients, chi-square tests, one- or two-sample t-tests or logistic regression analyses as appropriate. Non-parametric tests such as Spearman correlation coefficients, Fisher's exact tests and Wilcoxon rank sum test may be substituted if necessary. 95% percent confidence intervals will be constructed and selected results will be illustrated using figures and plots.

The log rank test, cox model or Chi-Square test will apply to access the association between PD-L1, CD3, CD4, CD8 expression and outcome (PFS, OS, ORR) where appropriate.

Frequency and severity of adverse events will be tabulated using counts and proportions detailing frequently occurring, serious and severe events of interest

All the analysis results are considered hypothesis generating.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with combination of nivolumab and XL184 (arm A, arm C) or nivolumab alone (arm B).

13.6.2 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 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 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 4-9 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 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses 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 sub analyses 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 (<i>e.g.</i> 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 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **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.

These are the things that you as a healthcare provider need to know:

XL184(cabozantinib) interacts with a certain specific enzyme in your liver, a certain transport protein that helps move drugs in and out of cells, and the heart's electrical activity (QTc prolongation) .

- The enzyme in question is **CYP 3A4**. XL184 (cabozantinib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
- The protein in question are **P-glycoprotein (P-gp) and MRP2**. XL184 (cabozantinib) is an inhibitor of P-gp and may be affected by other drugs that are “substrates.” XL184 is also a substrate of MRP2 and may be affected by other drugs that are “inhibitor” or “inducers” of MRP2.
- XL184 (cabozantinib) may affect the heart's electrical activity causing QTc prolongation. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

XL184 (cabozantinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

XL184 (cabozantinib) must be used very carefully with other medicines that use certain **liver enzyme, transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **“strong inducers/inhibitors of CYP3A4, substrate of P-gp, or any medicine associated with greater risk for having QTc prolongation.”**

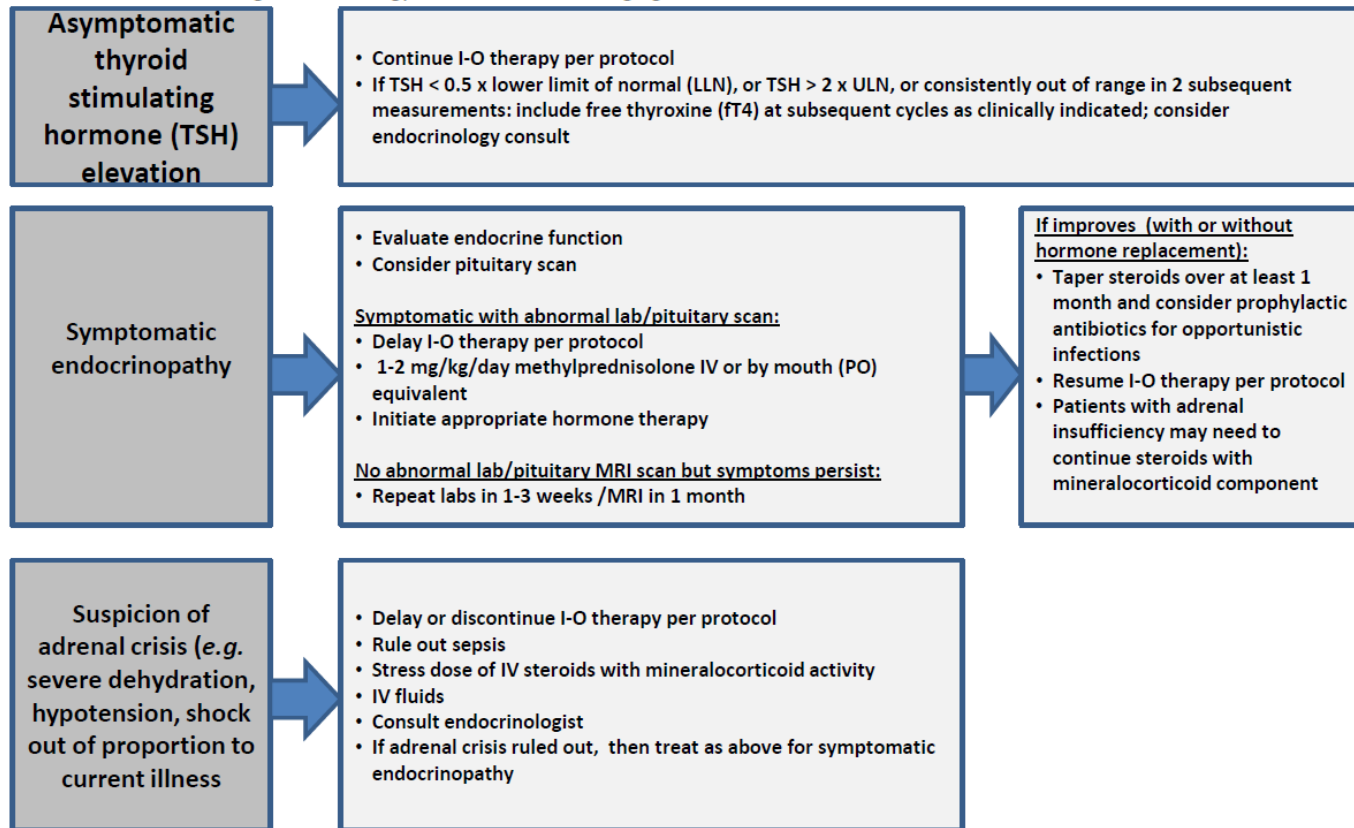
- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Do not drink or eat grapefruit/juice or Seville oranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

<p>STUDY DRUG INFORMATION WALLET CARD</p> <p>You are enrolled on a clinical trial using the experimental study drug _____. This clinical trial is sponsored by the NCI, _____ may interact with drugs that are processed by your liver, or use certain transport proteins in your body or affect the electrical activity of your heart. Because of this, it is very important to:</p> <ul style="list-style-type: none"> ➤ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➤ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) 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. 	<p>XL184 (cabozantinib) must be used very carefully with other medicines that interact with CYP3A4 enzyme, transporter proteins (P-gp) and MRP2, or drugs that may trigger your heart's electrical activity (QTc prolongation).</p> <ul style="list-style-type: none"> ➤ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered “strong inducers/inhibitors CYP3A4; P-gp substrates; or drugs that cause risks for QTc prolongation.” ➤ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➤ Your study doctor's name is _____ and can be contacted at _____.
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APPENDIX C MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

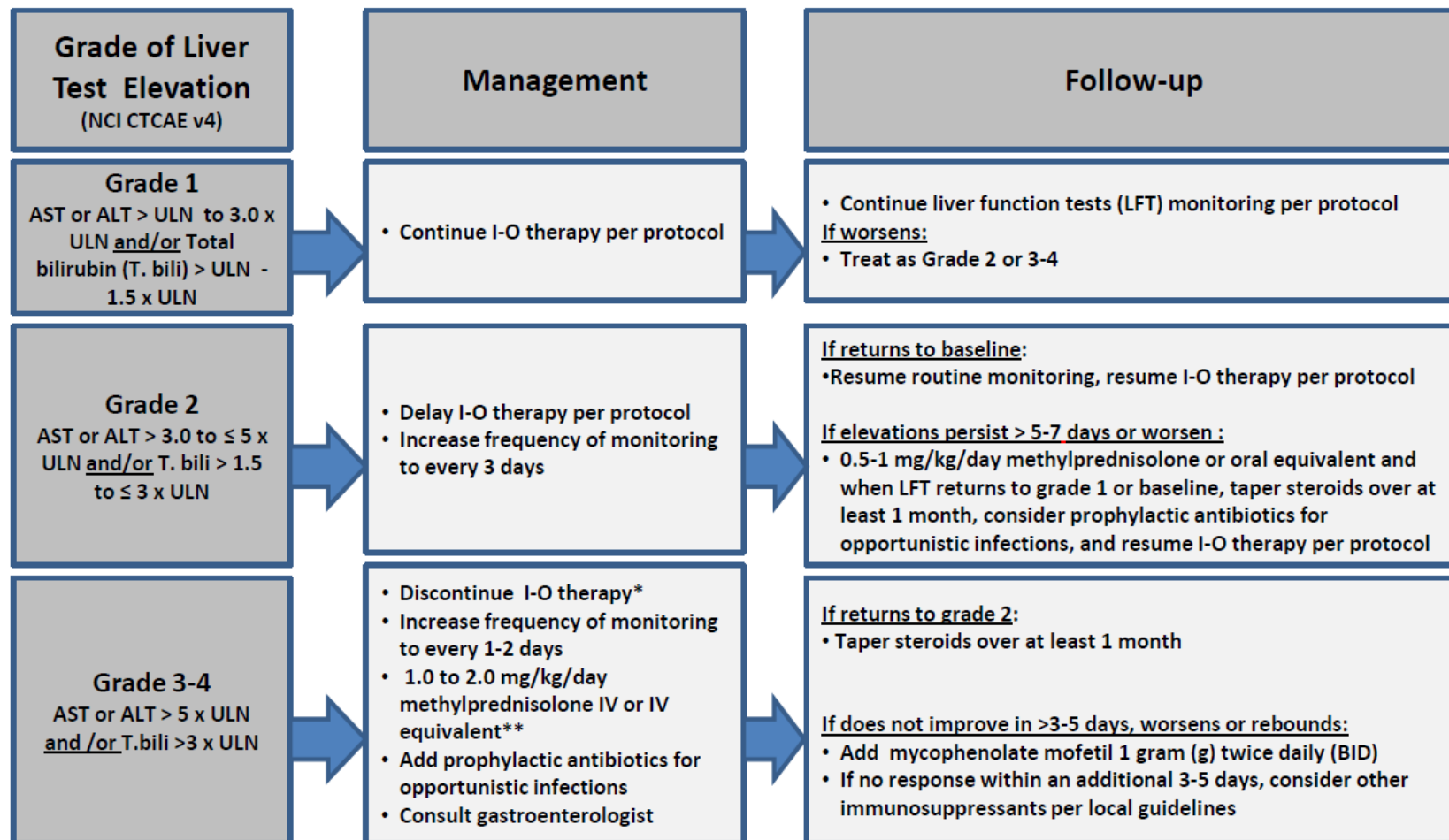
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



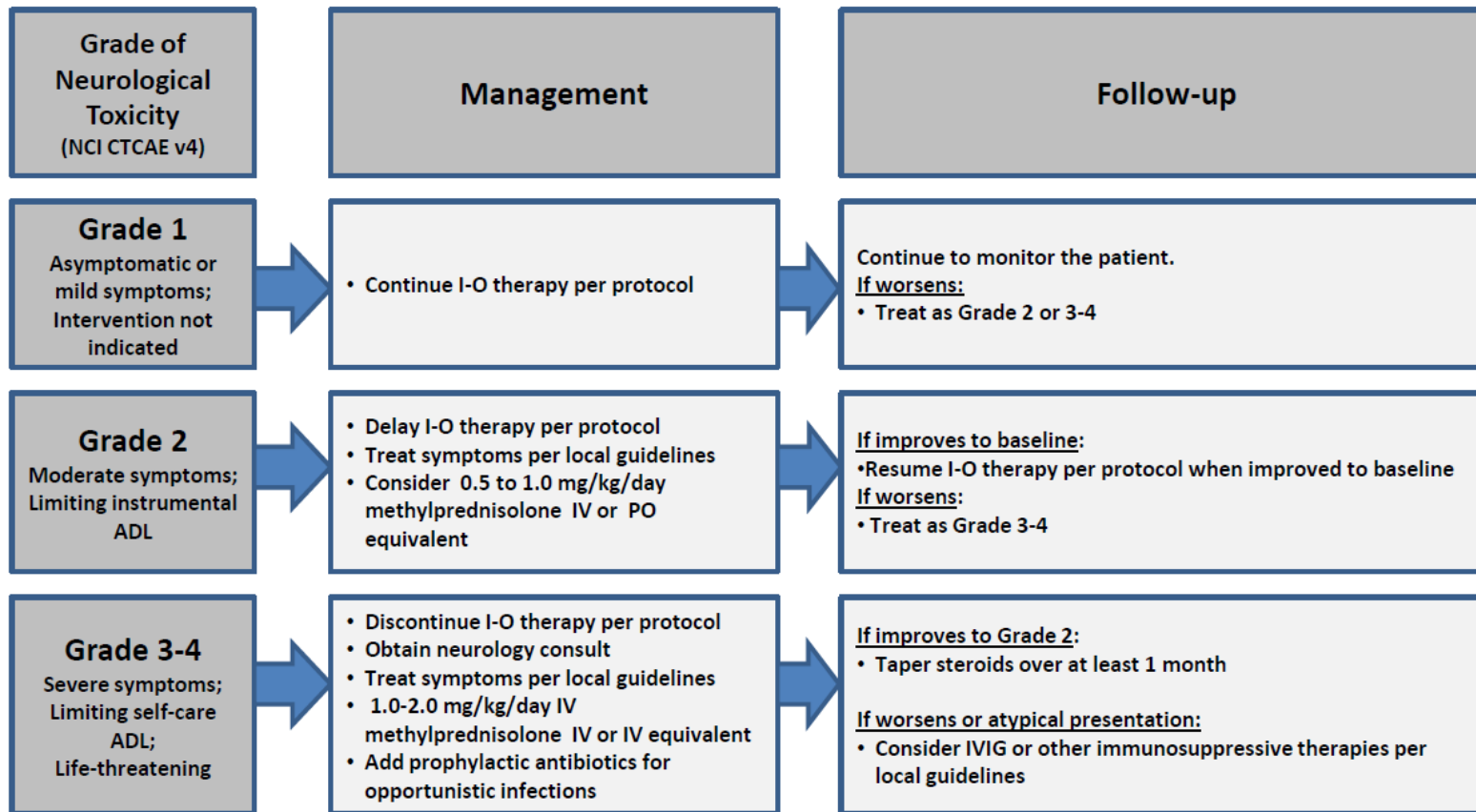
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Neurological Adverse Event Management Algorithm

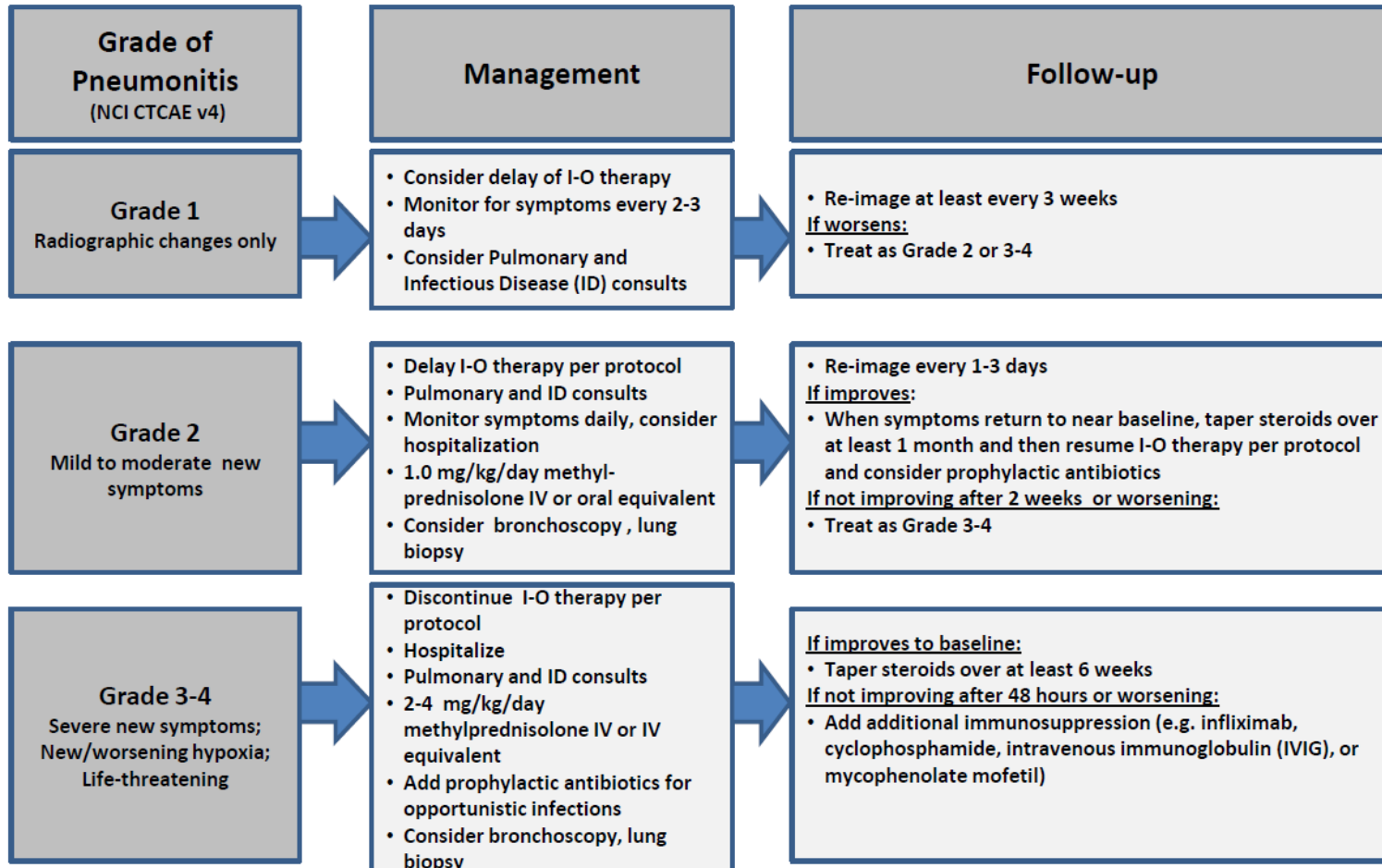
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

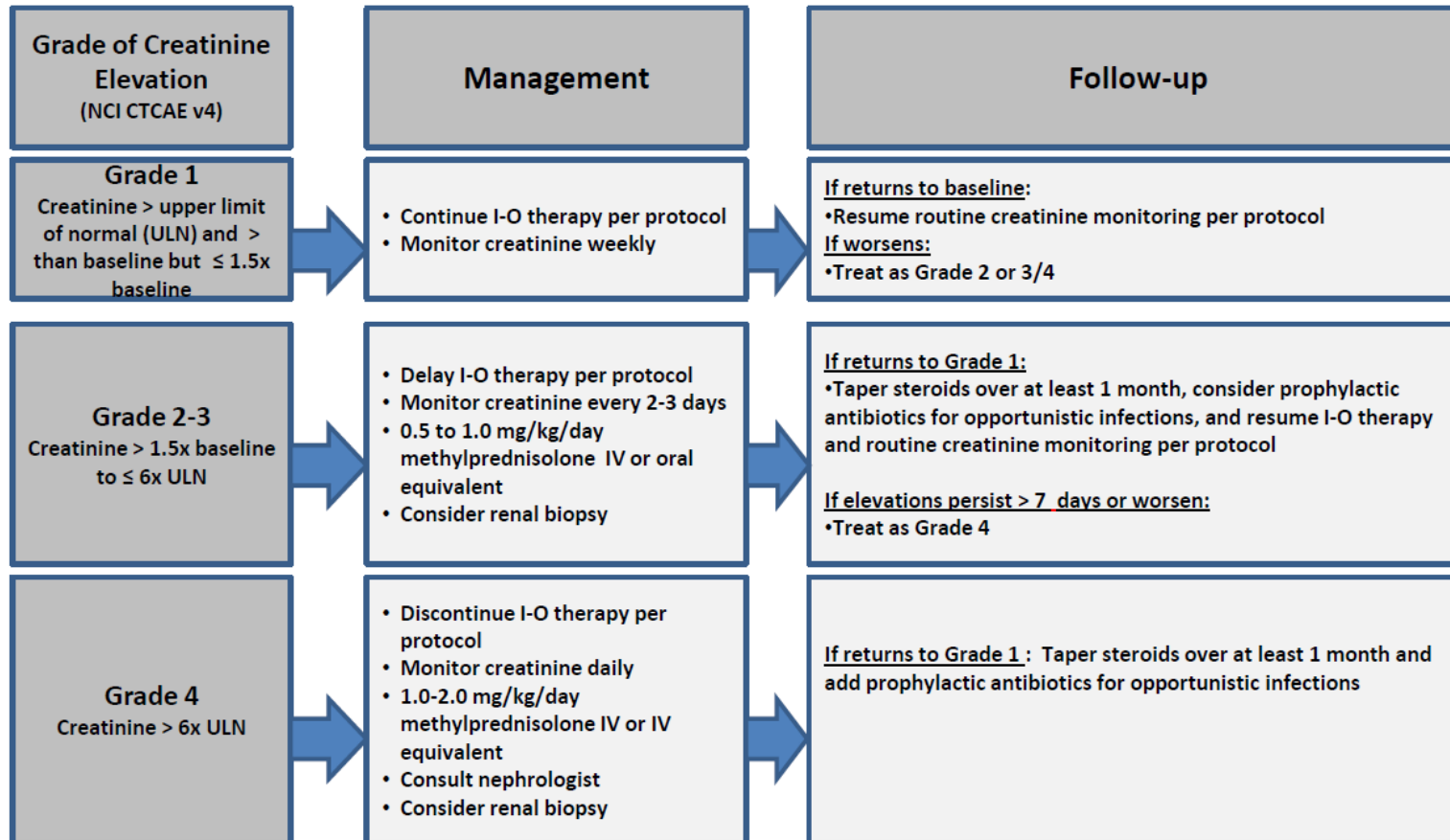
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

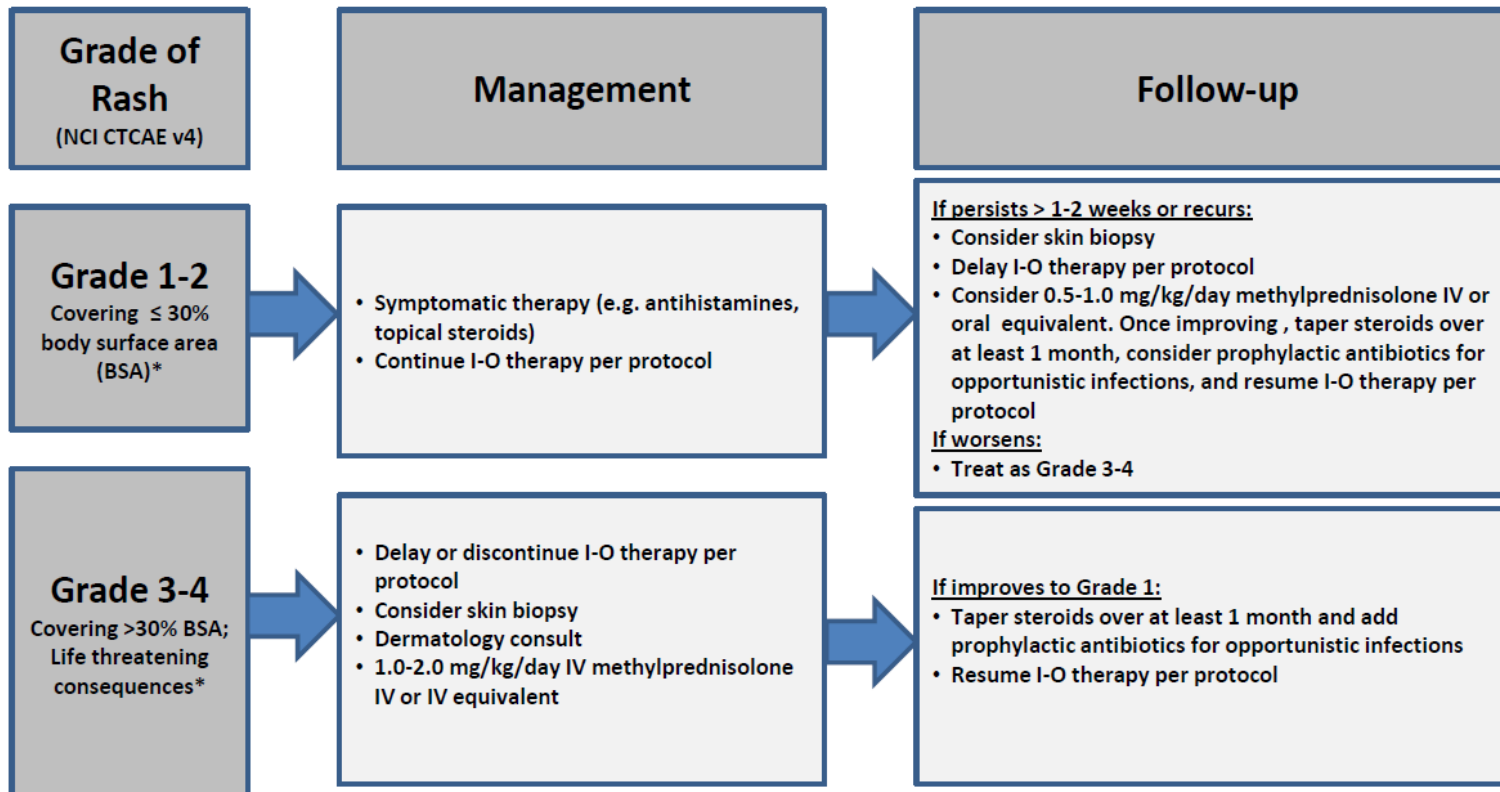
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

APPENDIX D PATIENT'S STUDY DRUG DIARY

Cabozantinib

CTEP-assigned Protocol # 10104 Local Protocol # PHL-099
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Today's Date _____ Patient Initials _____ Patient Study ID _____

INSTRUCTIONS

1. Complete one form for each cycle of treatment.
2. You will take **20 mg** Cabozantinib 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 Cabozantinib.
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 Cabozantinib 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.
8. If you miss or skip a dose for any reason, do not make up that missed dose if it is discovered within 12 hours of the next planned dose. Record that you took 0 pills that day.
9. If you vomit after taking your medication, do not re-take any tablets. Make a note in the Comments section.

Day	Date	Time of Dose	# of Cabozantinib pills taken	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:				
Total number of tablets taken:				
Start date for this cycle: _____				
End date for this cycle: _____				
Date patient was removed from study: _____				
The above information has been reviewed with the patient.				
Physician/Nurse Signature: _____				
Date: _____				

APPENDIX F PATIENT'S BLOOD PRESSURE MONITORING DIARY

CTEP-assigned Protocol # 10104 Local Protocol # PHL-099
--

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

INSTRUCTIONS:

1. You will be instructed by your nurse or physician on how to use the blood pressure machine provided to you.
2. Remain seated while you take your blood pressure.
3. Record the date, and the reading on the machine.
4. If you have any comments you would like to make, please record them in the Comments column.
5. 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 direction over the error, but on a separate line next to the error.

Day	Date	Blood Pressure	Comments
1.		/	
2.		/	
3.		/	
4.		/	
5.		/	
6.		/	
7.		/	
8.		/	
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23.		/	
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26.		/	
27.		/	
28.		/	
Physician's Office will complete this section:			
Start date for this cycle: _____			
End date for this cycle: _____			
The above information has been reviewed with the patient.			
Physician/Nurse Signature: _____			
Date: _____			

APPENDIX G – PATHOLOGY VERIFICATION FORM

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the ETCTN Biorepository.

If a pathology report is not available for the biopsy, a copy of the radiology report or operative report from the biopsy procedure must be sent to the ETCTN Biorepository. A completed copy of this appendix (i.e., Biopsy Pathology Verification) must also be submitted to the ETCTN Biorepository.

Note: If this information is not provided with the biopsy specimen, it will not be accepted by the ETCTN Biorepository.

Please have the Pathologist responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): **Primary** **Metastatic**

Time point (circle one): **Baseline** **Cross-Over** **Progression**

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

Pathologist's Signature

Date