To: CTEP Protocol and Information Office

From: Bhavana Konda, M.D.

Date: 08/17/2022

Re: Review of Amendment #10 of Protocol #10240: "Phase II Study of XL184 (Cabozantinib) in Combination with Nivolumab and Ipilimumab (CaboNivoIpi) in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Whose Cancer Progressed After One Prior VEGFR-Targeted Therapy"

PROTOCOL - SUMMARY OF CHANGES

I. OSU and CTEP Review Changes, 01/28/2021

#	Section	Comment(s)
1.	All Pages	• Updated Heading and Version Number.
2.	Title Page	• Updated Protocol Version Date and Amendment Number.
3.	5.6	• Modified Protocol to allow requesting tumor genotyping and PDL1 reports from all participating institutions: Added: As of August 20, 2021, stage 1 of the study reached its target accrual. Interim analysis for efficacy revealed that the study did not reach its pre-specified threshold for efficacy. The study therefore did not proceed to stage 2. As correlative studies were proposed to only be done in stage 2 of the study, no specimens for biomarkers were collected. In general, tumor genotyping (limited or broad) along with PD L1 and TMB testing is commonly performed at several institutions a patient's disease course to evaluate for actionable genomic alterations. For example, the presence of BRAF V600E mutation appears to portend an aggressive tumor biology and a poor prognosis [1]. In order to correlate study treatment response (RECIST v1.1) with tumor mutation status and PD L1 status, redacted tumor genotyping reports including tumor mutation burden and PDL1 status will be requested if these are available or will be available.

NCI Protocol #: 10240

Local Protocol #: OSU-19088

ClinicalTrials.gov Identifier: NCT 03914300

Title: Phase II Study of XL184 (cabozantinib) in combination with Nivolumab and Ipilimumab (CaboNivoIpi) in Patients with Radioiodine-refractory Differentiated Thyroid Cancer whose Cancer Progressed after One Prior VEGFR-Targeted Therapy

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NCI-Supplied Agents: XL184 (cabozantinib) (NSC 761968)
Nivolumab (BMS-936558, MDX-1106, ONO-4538) (NSC 748726)
Ipilimumab (BMS-734016, MDX-010) (NSC 732442)

IND #: [redacted]
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Amendment #6 / June 23, 2020
Amendment #7 / August 13, 2020
Amendment #8 / January 28, 2021
Amendment #9 / February 25, 2021 (Disapproved)
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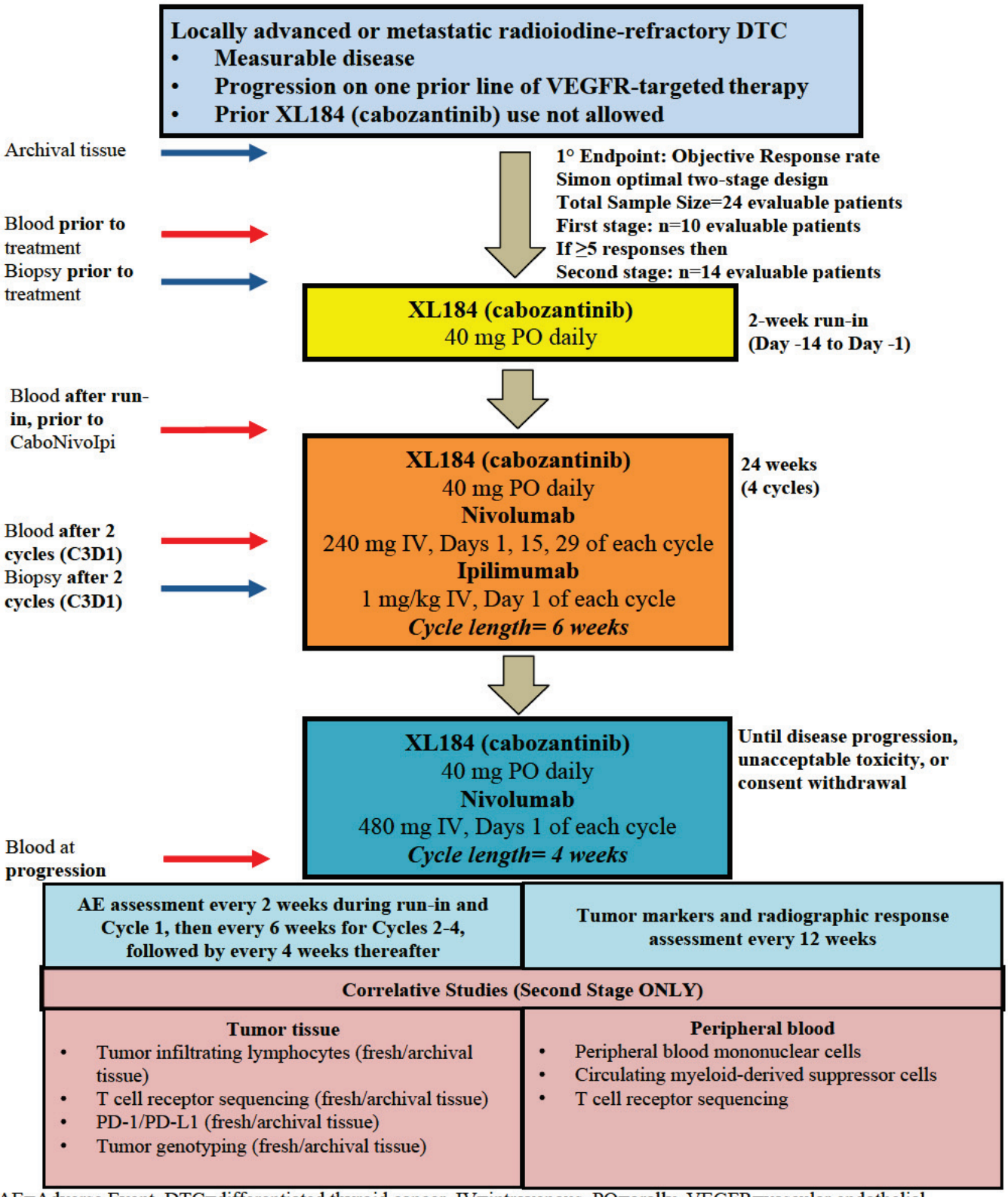
SCHEMA



AE=Adverse Event, DTC=differentiated thyroid cancer, IV=intravenous, PO=orally, VEGFR=vascular endothelial growth factor receptor

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the objective response rate, defined as the proportion of patients who have had a partial response (PR) or complete response (CR) within the first 6 months after initiation of therapy with XL184 (cabozantinib), nivolumab, and ipilimumab (CaboNivoIpi).

1.2 Secondary Objectives

1.2.1 To assess duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS).

1.2.2 To assess tolerability and adverse events of CaboNivoIpi in patients with differentiated thyroid cancer (DTC).

1.3 Exploratory Objectives

1.3.1 To correlate treatment response (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) with tumor mutation status.

1.3.2 To correlate treatment response (RECIST v1.1) with frequency of tumor infiltrating lymphocytes in biopsies taken pre-treatment and after 12 weeks of CaboNivoIpi therapy.

1.3.3 To evaluate the effect of CaboNivoIpi on T cell receptor (TCR) repertoire and to identify the frequency of shared T cell clones between tumor and peripheral blood.

1.3.4 To evaluate the effect of XL184 (cabozantinib) alone and of the CaboNivoIpi combination on peripheral blood mononuclear cells (PBMCs) and to correlate their frequency with treatment response (RECIST v1.1).

1.3.5 To evaluate the effect of XL184 (cabozantinib) alone and of the CaboNivoIpi combination on myeloid-derived suppressor cells (MDSCs) and to correlate their frequency with treatment response (RECIST v1.1).

1.3.6 To correlate treatment response (RECIST v1.1) with programmed cell death protein 1 (PD-1) / programmed cell death-ligand 1 (PD-L1) expression in the primary/metastatic tumor.

2. BACKGROUND

2.1 Study Diseases

Thyroid cancer is the most common endocrine neoplasm, with 53,990 new cases estimated to be diagnosed in the United States in 2018 (American Cancer Society, 2018). Thyroid cancers are histologically classified into: DTC, which includes papillary thyroid cancer (PTC); follicular thyroid cancer (FTC), or Hürthle cell thyroid cancer (HTC); medullary thyroid cancers (MTC); and anaplastic thyroid cancers (ATC) (Woyach and Shah, 2009). DTC are derived from the thyroid follicular cell and are by far the most common subtype, accounting for over 90 percent of all newly diagnosed cases. Standard of care therapy for metastatic DTC include surgery, radioactive iodine (RAI), and thyroid-stimulating hormone (TSH) suppression with levothyroxine. While most patients with DTC have high long-term survival rates, those who develop RAI-refractory disease have limited treatment options. Vascular endothelial growth factor receptor (VEGFR)-mediated activation of angiogenic signaling pathways, and aberrant intracellular signaling in the MAPK and PI3K/AKT/mTOR pathways play an important role in the pathogenesis of these tumors, and inhibition of these pathways has been a successful therapeutic strategy in these patients.

The multi-kinase inhibitors sorafenib and lenvatinib have demonstrated ORRs of 12% (Brose *et al.*, 2014) and 65% (Schlumberger *et al.*, 2015), respectively, in phase 3 trials with RAI-refractory DTC and are the only drugs approved by the United States Food and Drug Administration (FDA) in these patients. Resistance to these agents is inevitable, precluding durable responses, with median PFS of 10.8 months with sorafenib (Brose *et al.*, 2014) and 18.3 months with lenvatinib (Schlumberger *et al.*, 2015).

2.2 CTEP IND Agents

2.2.1 XL184 (cabozantinib)

XL184 (cabozantinib, Cabometyx®, Cometriq®) is an oral multi-targeted inhibitor of receptor tyrosine kinases (RTKs) with half-maximal inhibitory concentrations (IC_{50}) ranging from 2 to 101 nM (Cabozantinib Investigator's Brochure, 2018). The targets of XL184 (cabozantinib) include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely VEGFR2, MET, AXL, and RET. Other recognized targets of XL184 (cabozantinib) include ROS1, TRKA, TRKB, TIE2, TYRO3, and MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely related RTKs KIT and FLT-3. The mode of action for XL184 (cabozantinib) is similar to other drugs targeting RTKs: binding in a fully reversible manner to a region of the kinase domain (including the ATP-binding site) which forces the kinase activation loop into a pseudo-inactive conformation, thereby inhibiting subsequent catalytic activity. Both MET and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and *in vivo* pharmacodynamic activity of XL184 (cabozantinib) against 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 repair (Christensen *et al.*, 2005). Dysregulation of RTKs by

mutation, gene rearrangement, gene amplification, or overexpression of the receptor or its ligands have been implicated as causative factors in the development and progression of numerous cancers.

The proto-oncogene *MET* encodes the high-affinity receptor for hepatocyte growth factor (HGF) (also known as scatter factor [SF]) (Christensen *et al.,* 2005). MET and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc*.), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Cabozantinib Investigator's Brochure, 2018). MET-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking MET and HGF as causative or progression factors in human cancers includes the overexpression of both receptors and ligands in neoplasms relative to surrounding tissues, the correlation of receptor and ligand overexpression with disease severity and outcome, and genetic alteration of *MET* by mutation or gene amplification in multiple cancer types (Christensen *et al.*, 2005). Introduction of MET and HGF, or mutant MET into cell lines conferred the properties of tumorgenicity and metastatic propensity on engineered cells and introduction of MET or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms. The inhibition of MET or HGF function with dominant-negative receptors, antibody antagonists (both MET and HGF), or biologic antagonists (*e.g.*, NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo.

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated MET activity (Liu *et al.*, 2010), either by means of MET kinase overexpression (Comoglio *et al.*, 2008), activating MET gene mutations and/or amplification (Comoglio *et al.*, 2008; Jeffers *et al.*, 1997; Schmidt *et al.*, 1997), or increased autocrine and/or paracrine secretion of the MET ligand, HGF/SF (Birchmeier *et al.*, 2003; Boccaccio and Comoglio, 2006). These alterations have been implicated in tumor progression and metastasis, and high constitutive activation of MET has been correlated with poor clinical prognosis (Birchmeier *et al.*, 2003).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Roskoski, 2008). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (Tugues *et al.*, 2011). High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer (TNBC) and poor survival.

2.2.1.1 Nonclinical Development of XL184 (cabozantinib)

2.2.1.1.1 Nonclinical *In Vivo* Activity

Data from pharmacodynamic experiments have shown that XL184 (cabozantinib) inhibits MET and VEGFR2 *in vivo*. Oral administration of XL184 (cabozantinib) resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, the duration of action for XL184 (cabozantinib) was sustained, with >50% inhibition observed for >8 hours post-dose at a single dose level of 100 mg/kg (Yakes *et al.*, 2011). In addition, oral administration of XL184 (cabozantinib) resulted in blockade of phosphorylation of mutationally activated RET in TT human MTC xenografts grown in nude mice (Bentzien *et al.* 2013).

Treatment with XL184 (cabozantinib) results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects (Yakes *et al.* 2011). These effects translate into significant tumor growth inhibition or tumor regression after XL184 (cabozantinib) treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and glioblastoma.

Inhibition of the VEGF signaling pathway alone was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of neuroendocrine pancreatic cancer that spontaneously develops aggressive tumors (Pàez-Ribes *et al.* 2009). Treatment with XL184 (cabozantinib) for 3 weeks, from age 14 to 17 weeks, significantly prevented formation of liver metastases in the RIP-Tag2 model compared with anti-VEGF treatment or vehicle alone ($P<0.05$ *vs.* vehicle and anti-VEGF antibody). The number of liver metastases was 5-fold greater in anti-VEGF antibody-treated animals compared with vehicle-treated animals, and no liver metastases were detected in XL184 (cabozantinib)-treated animals. In addition, treatment with XL184 (cabozantinib) from age 14 to 20 weeks improved survival. Median survival was 14.7 weeks for vehicle-treated animals (n=12) and 16.4 weeks for anti-VEGF antibody-treated animals (n=7; $P<0.05$ *vs.* vehicle), and all XL184 (cabozantinib)-treated animals survived for the full 20 weeks of observation (n=6; $P<0.05$ *vs.* vehicle and anti-VEGF antibody).

2.2.1.1.2 Nonclinical Pharmacokinetics

Nonclinical pharmacokinetics (PK) of XL184 (cabozantinib) was studied in mice, rats, dogs, and monkeys (Cabozantinib Investigator's Brochure, 2018). Oral bioavailability was comparably high in rats (80-86%), dogs (87%) and monkeys (73%) and moderately high in mice (42-51%) when XL184 (cabozantinib) was formulated with an aqueous vehicle. In rats, systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC] from 0 hours to a specific post-dose time [AUC_{0-t}]) increased less than dose-proportionally in association with single XL184 (cabozantinib) oral doses, and generally dose-proportionally with moderate accumulation (≤4-fold) following repeat daily oral dosing. In dogs, systemic drug exposure parameters increased less than dose-proportionally with increasing single XL184 (cabozantinib) oral doses, and generally dose-proportionally with little or no accumulation (≤2-fold increase) following repeat daily dosing.

2.2.1.1.3 Toxicology

Toxicity associated with oral administration of XL184 (cabozantinib) was characterized in definitive (Good Laboratory Practice [GLP]-compliant) single-dose and repeat-dose studies in mice, rats, and dogs; a fertility study in rats; embryotoxicity/teratogenicity studies in rats and rabbits; juvenile toxicity studies in rats; in vitro and in vivo genotoxicity bioassays; and an in vitro phototoxicity study (Cabozantinib Investigator's Brochure, 2018). Target tissues for XL184 (cabozantinib)-related toxicity identified in these studies include gastrointestinal (GI) tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, kidney, and skin. Histopathologic changes were also present in bone, central nervous system (CNS) tissues and liver/gall bladder. Adverse findings associated with XL184 (cabozantinib) administration were observed in both rodent and non-rodent species and were generally dose-related and often correlative with clinical signs and/or clinical pathology parameter changes reflective of associated target tissue histopathologic findings. Adverse findings were generally reversible upon discontinuation of treatment. In definitive reproductive and developmental toxicity studies, XL184 (cabozantinib) reduced fertility in male and female rats, was embryotoxic in rats, produced a fetal soft-tissue malformation (small spleen) in rabbits, and produced fetal external malformations (cleft palate/lip, dermal aplasia and kinked or rudimentary tail) in rats. XL184 (cabozantinib) was negative in *in vitro* bacterial and mammalian genotoxicity, clastogenicity, and phototoxicity bioassays. The metabolite present at highest plasma concentrations in humans administered XL184 (cabozantinib), EXEL-1644, was negative in an *in vitro* bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats dosed subcutaneously with EXEL-1644 for 2 weeks.

2.2.1.2 Clinical Development of XL184 (Cabozantinib)

Patients have received XL184 (cabozantinib) in 18 Exelixis-sponsored clinical trials, 35 investigator-sponsored studies, and 19 National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)-sponsored studies (Cabozantinib Investigator's Brochure, 2018). The maximum tolerated dose (MTD) on once daily oral (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent by weight). Detailed information for each of these studies, including pharmacokinetic data, can be found in the XL184 (cabozantinib) Investigator's Brochure (2018). Safety and efficacy information from the 2018 XL184 (cabozantinib) Investigator's Brochure is summarized below.

2.2.1.2.1 Safety

Across Exelixis-sponsored studies with single-agent XL184 (cabozantinib), the most frequently observed adverse events (AEs) (≥20% of patients), regardless of causality, were diarrhea, fatigue, decreased appetite, nausea, palmar-plantar erythrodysaesthesia syndrome (PPES), vomiting, weight loss, constipation, hypertension, dysgeusia, dysphonia, and asthenia (Investigator's Brochure, 2018). The most frequently observed serious AEs (SAEs) (≥2% of patients), regardless of causality, were pulmonary embolism (PE), pneumonia, general physical health deterioration, vomiting, nausea, dehydration, anemia, and diarrhea. In these single-agent studies, 42 patients had grade 5 AEs that were assessed as related to study treatment. The only

related grade 5 AEs that occurred more than once were PE (n=5), hepatic failure (n=3); death (unspecified; n=3), hemorrhage (n=2), respiratory failure (n=2), sudden death (n=2), and GI perforation (n=2). In investigator-sponsored and CTEP-sponsored trials, the most frequent SAEs were embolism, nausea, dyspnea, dehydration, fatigue, and hypophosphatemia.

2.2.1.2.2 Efficacy

The clinical activity of XL184 (cabozantinib) has been evaluated in pivotal trials in renal cell cancer (RCC), hepatocellular carcinoma (HCC), MTC, and castrate-resistant prostate cancer (CRPC) (Cabozantinib Investigator's Brochure, 2018). In phase 1 and 2 studies, XL184 (cabozantinib) has also demonstrated findings consistent with broad clinical antitumor activity in multiple tumor types.

Phase 3, randomized, open-label, active-controlled Study XL184-308 was conducted in 658 patients (330 XL184 [cabozantinib], 328 everolimus) with advanced RCC who had received prior treatment with at least one VEGFR-tyrosine kinase inhibitor (TKI) (Cabozantinib Investigator's Brochure, 2018). XL184 (cabozantinib) demonstrated statistically significant improvements in the primary endpoint (PFS) and both secondary endpoints (ORR and OS) compared with the standard-of-care control treatment (everolimus). In the primary PFS analysis performed in the first 375 patients randomized, the hazard ratio (HR) adjusted for stratification factors was 0.58 (95% confidence interval [CI], 0.45-0.74; stratified logrank $P<0.0001$), and the Kaplan-Meier estimates for median PFS were 7.4 months in the XL184 (cabozantinib) arm *vs.* 3.8 months in the everolimus arm. The PFS analysis was repeated in all 658 patients, and the results (stratified HR = 0.51 [95% CI, 0.41-0.62]) were similar to those obtained from the initial analysis. In the primary analysis of ORR, the ORRs for the XL184 (cabozantinib) and everolimus arms were 17% (95% CI, 13%-22%) and 3% (95% CI, 2%-6%), respectively (unstratified $P<0.0001$). Kaplan-Meier estimates for median OS were 21.4 months in the XL184 (cabozantinib) arm and 16.5 months in the everolimus arm. Results for extensive subgroup analyses of PFS, OS, and ORR showed a consistent benefit for XL184 (cabozantinib) treatment versus everolimus.

Phase 2, randomized, open-label, active-controlled Study A031203 (CABOSUN), was sponsored by CTEP and conducted by The Alliance for Clinical Trials in Oncology (Alliance) in 157 patients (79 XL184 (cabozantinib), 78 sunitinib) with untreated clear cell locally advanced or metastatic RCC of intermediate or poor risk (Cabozantinib Investigator's Brochure, 2018). Compared with the standard-of-care control treatment, sunitinib, XL184 (cabozantinib) demonstrated statistically significant improvements in the primary endpoint of PFS and the secondary endpoint of ORR as well as a non-significant trend of improvement in the secondary endpoint of OS. In the primary analysis performed by the Alliance, a benefit in PFS per investigator assessment was demonstrated for XL184 (cabozantinib) compared with sunitinib. In Exelixis-initiated retrospective primary PFS and secondary ORR analyses based on blinded assessments, there was a statistically significant improvement in PFS for patients in the XL184 (cabozantinib) arm compared with the sunitinib arm (HR=0.48 [95% CI, 0.31-0.74]; stratified 2-sided logrank $P=0.0008$); median PFS was 8.6 months in the XL184 (cabozantinib) arm and 5.3 months in the sunitinib arm. Further, ORR (secondary endpoint) per IRC in the XL184 (cabozantinib) arm was improved compared with the sunitinib arm: 20% *vs.* 9% (stratified 2-

sided *P*=0.0406). In an OS (secondary endpoint) analysis of data, the Kaplan-Meier estimates for median OS were 30.3 months in the XL184 (cabozantinib) arm *vs.* 21.0 months in the sunitinib arm (stratified HR adjusted for stratification factors was 0.74 [95% CI, 0.47-1.14]; stratified 2-sided logrank *P*=0.1700).

A total of 707 patients (470 XL184 (cabozantinib), 237 placebo) with advanced HCC who had received prior treatment with sorafenib were enrolled in phase 3, randomized, double-blinded, placebo-controlled Study XL184-309 through the 01 June 2017 database cutoff date (Cabozantinib Investigator's Brochure, 2018). In the study, XL184 (cabozantinib) demonstrated a robust and statistically significant improvement in OS, PFS, and ORR. The analysis of duration of OS (primary endpoint) demonstrated a statistically significant improvement for patients in the XL184 (cabozantinib) arm compared with the placebo arm: the HR, adjusted for stratification factors was 0.76 (95% CI, 0.63-0.92; stratified logrank *P*=0.0049). The Kaplan-Meier estimates for median OS were 10.2 months in the XL184 (cabozantinib) arm *vs.* 8.0 months in the placebo arm. A statistically significant improvement in PFS for patients in the XL184 (cabozantinib) arm compared with the placebo arm was also observed. The HR, adjusted for stratification factors was 0.44 (95% CI, 0.36-0.52; stratified logrank *P*<0.0001). The Kaplan-Meier estimates for median PFS were 5.2 months in the XL184 (cabozantinib) arm *vs.* 1.9 months in the placebo arm. The ORR was 4% and 0.4% for patients in the XL184 (cabozantinib) and placebo arms, respectively (stratified Cochran-Mantel-Haenszel [CMH] test *P*=0.0086).

Phase 3, randomized, double-blind, placebo-controlled study XL184-301 was conducted in 330 MTC patients (219 XL184 (cabozantinib), 111 placebo) (Cabozantinib Investigator's Brochure, 2018). An increase in PFS (primary endpoint) was seen, with a median PFS of 11.2 months in the XL184 (cabozantinib) arm compared with 4.0 months for placebo (HR=0.28 [95 CI, 0.19-0.40]). For the secondary endpoint of ORR, confirmed PRs occurred in 28% of XL184 (cabozantinib)-treated patients and no placebo-treated patients and responses were durable (median DOR=14.6 months). The final analysis of the secondary endpoint of OS included 218 deaths and showed a non-significant trend for improved median OS in the XL184 (cabozantinib) arm compared with the placebo arm (26.6 months *vs.* 21.1 months; HR=0.85 [95% CI, 0.64-1.12]; *P*=0.2409). Because MTC is a relatively rare disease, the study was not designed to be large enough to provide high power to detect the minimum clinically significant difference in the secondary endpoint of OS. The subgroup analysis of patients with a RET M918T mutation revealed a larger improvement in OS for the XL184 (cabozantinib) arm: the median OS was 44.3 months for the XL184 (cabozantinib) arm *versus* 18.9 months for the placebo arm (HR=0.60 [95% CI, 0.38-0.94]; *P*=0.0255, not adjusted for multiple subgroup analyses). In all patients, the median duration of XL184 (cabozantinib) treatment was 10.8 months, and the 75th percentile for duration of treatment was 24.8 months. The maximum duration of treatment was 59.4 months at the data cutoff of the final OS analysis.

In addition to RCC, HCC, and MTC, XL184 (cabozantinib) has demonstrated findings consistent with broad clinical antitumor activity in multiple other tumor types (Cabozantinib Investigator's Brochure, 2018). Observations of clinical activity have included decrease of soft tissue tumor lesions including visceral metastases, reduction in serum markers of bone resorption and formation, and reduction in circulating tumor cells (CTCs) in patients with prostate cancer.

Though they failed to meet their respective primary endpoints of OS and pain response, phase 3 studies XL184-307 and XL184-306 demonstrated clinical activity in CRPC including effects on PFS (XL184-307) and bone scan response (both studies). Clinical antitumor activity has also been observed in company-sponsored phase 1 and 2 studies across indications including non-small cell lung cancer (NSCLC), breast cancer, melanoma, ovarian cancer, glioblastoma (GB), and differentiated thyroid cancer (DTC).

2.2.1.3 Marketing Experience

XL184 (cabozantinib) is approved in the United States as Cometriq® for the treatment of progressive, metastatic MTC and as Cabometyx® for advanced RCC (Cabozantinib Investigator's Brochure, 2018). As of February 2018, commercial exposure in the post-marketing setting to Cometriq® was estimated as >2000 patients and exposure to Cabometyx® was estimated as >12000 patients. No new safety signals associated with Cometriq® or Cabometyx® were observed in post-marketing.

2.2.2 Nivolumab

Nivolumab (BMS-936558, MDX-1106, ONO-4538, Opdivo®) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human PD-1, cluster of differentiation 279 (CD279) cell surface membrane receptor (Nivolumab Investigator's Brochure, 2018). 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 a variety of cancers. The combination of nivolumab and ipilimumab, an anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) agent, in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in patients with melanoma (Wolchok *et al*., 2013). See Section 2.2.3 for more information about ipilimumab.

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer (Nivolumab Investigator's Brochure, 2018). 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 OS with or without radiographic responses or improved 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) (Nivolumab Investigator's Brochure, 2018). PD-1 is transiently, but highly expressed on activated T-cells and functions 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 (T-cell immunoglobulin mucin 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-β).

Two ligands specific for PD-1 have been identified: 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 treatment (Woo *et al*., 2012). 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 melanoma (Taube *et al*., 2012), renal (Thompson *et al*., 2004; Thompson *et al*., 2005; Thompson *et al*., 2006), esophageal (Ohigashi *et al*., 2005), gastric (Wu *et al*., 2006), ovarian (Dong *et al*., 2003), pancreatic (Nomi *et al*., 2007), lung (Zitvogel *et al*., 2006), and other cancers (Nivolumab Investigator's Brochure, 2018).

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 × 4) resulted in decreased viral loads and increased survival along with expanded T-cells with increased T-cell functionality.

2.2.2.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Nivolumab Investigator's Brochure, 2018). 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 dissociation constant (K_d) of 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.

2.2.2.2 Clinical Development of Nivolumab

Nivolumab has demonstrated clinical activity, and has been approved for use in NSCLC, melanoma, RCC, classical Hodgkin's Lymphoma (cHL), squamous cell carcinoma (SCC) of the head and neck, and urothelial carcinoma as monotherapy and in combination with ipilimumab and other therapeutics (Nivolumab Investigator's Brochure, 2018). It has also demonstrated activity in other tumor types. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in patients with advanced or metastatic melanoma, patients with advanced or metastatic NSCLC, patients with advanced RCC, and patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in PFS and ORR over ipilimumab monotherapy in patients with advanced or metastatic melanoma.

Nivolumab is also being evaluated in several other cancers, including small cell lung cancer (SCLC), gastric and esophageal cancer, hepatocellular carcinoma, colorectal cancer, GB, and Merkel cell carcinoma (MCC).

2.2.2.2.1 Pharmacokinetics

PK of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in C_{max} and AUC from time zero to infinity ($AUC_{0-\infty}$), with low to moderate inter-patient variability observed at each dose level (Nivolumab Investigator's Brochure, 2018). 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 nivolumab is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.2.2.2.2 Efficacy

In a randomized, open-label, phase 3 trial, patients with unresectable or metastatic melanoma who had progressed after treatment with ipilimumab were given either IV nivolumab (3 mg/kg every 2 weeks) or investigator's choice chemotherapy (ICC): dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 combined with carboplatin AUC=6 every 3 weeks) (Weber *et al.*, 2015). Of the first 120 patients treated with nivolumab, objective responses (CR or PR) were seen in 38 (31.7%) versus 5 (10.6%) out of 47 patients in the ICC arm. Grade 3-4 AEs related to nivolumab included increased lipase, increased alanine aminotransferase, anemia, and fatigue. Grade 3-4 drug-related SAEs were noted in 12 (5%) nivolumab-treated patients. No treatment-related deaths occurred.

In a phase 1/2 trial, patients with virus-positive and -negative solid tumors, including MCC, were given 240 mg nivolumab IV every 2 weeks (Nivolumab Investigator's Brochure, 2018). As of the February 16, 2017 data cutoff, of 25 patients with MCC who had received nivolumab, objective responses (PR or CR) were seen in 16 patients (64%, 95% CI 42.5%-82%). Median DOR, PFS, and OS have not been reached.

In a randomized, open-label, phase 3 trial, patients with recurrent SCCHN were given either IV nivolumab (3 mg/kg every 2 weeks) or standard systemic therapy (methotrexate, docetaxel, or cetuximab) (Ferris *et al.*, 2016). The median OS was 7.5 months (95% CI, 5.5-9.1 months) in the nivolumab group versus 5.1 months (95% CI, 4-6 months) in the group that received standard therapy. OS was significantly longer with nivolumab than with standard therapy (HR, 0.70 [97.73% CI, 0.51-0.96]; *P*=0.01), and the estimates of the 1-year survival rate were approximately 19% higher with nivolumab than with standard therapy (36.0% *vs.* 16.6%). The median PFS was 2 months (95% CI, 1.9-2.1 months) with nivolumab versus 2.3 months (95% CI, 1.9-3.1 months) with standard therapy (HR for disease progression or death, 0.89 [95% CI, 0.70-1.13]; *P*=0.32). The PFS rate at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Treatment-related AEs of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group. Physical, role, and social functioning was stable in the nivolumab group, whereas it was meaningfully worse in the standard-therapy group.

In an open-label, phase 2 trial, patients with recurrent or metastatic colorectal cancer assessed as MSI-high were given 3 mg/kg IV nivolumab every 2 weeks as monotherapy, or in combination with 1 mg/kg IV ipilimumab every 3 weeks for 4 doses followed by 3 mg/kg IV nivolumab every 2 weeks (Nivolumab Investigator's Brochure, 2018; Overman *et al.*, 2017). As of the September 19, 2016 data cut-off, 74 patients had received nivolumab monotherapy and 30 had received combination nivolumab/ipilimumab therapy. At a median follow-up of 12 months, 23 of 74 nivolumab-treated patients (31.1% [95% CI, 20.8%-42.9%]) achieved an objective response and 51 patients (69% [95% CI, 57%-79%]) had disease control for 12 weeks or longer. As of the data cut-off, median DOR had not yet been reached; all responders were alive, and eight had responses lasting 12 months or longer (Kaplan-Meier 12-month estimate, 86% [95% CI, 62%-95%]). Median PFS was 7.6 months (95% CI, 3 months-not reached [NR]). The 6- and 12-month PFS rates were 51.5% (95% CI, 38.9%-62.8%) and 45.6% (95% CI, 32.2%-58.1%), respectively. The 6- and 12-month OS rates were 83.4% (95% CI, 72.5%-90.2%) and 73.8% (95% CI, 59.8%-83.5%), respectively. The most common grade 3 or 4 drug-related AEs were increased concentrations of lipase (six patients, 8%) and amylase (two patients, 3%). Twenty-three patients (31%) died during the study; none of these deaths were deemed to be treatment related by the investigator. Out of 30 patients who had received nivolumab and ipilimumab combination therapy, 27 were evaluable for response (Nivolumab Investigator's Brochure, 2018). Of these, objective responses were seen in 9 patients (33.3%, 95% CI, 18.6%-50.9%). The 6-month PFS rate was 66.6% (95% CI, 45.5%-81.1%) and the 6-month OS rate was 85.1% (95% CI, 65.0%-94.2%).

2.2.2.2.3 Toxicology

An MTD of nivolumab was not reached at any dose up to 10 mg/kg (Topalian *et al*., 2012; Nivolumab Investigator's Brochure, 2018). There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab (Nivolumab Investigator's Brochure, 2018). A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

The overall safety experience with nivolumab is based on experience in approximately 16,900 patients who received either nivolumab alone or in combination with other therapeutics (Nivolumab Investigator's Brochure, 2018). In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in patients with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

2.2.2.2.4 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 count (Wolchok *et al*., 2013). 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-gamma (IFN- γ), indoleamine 2,3 dioxygenase (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.

2.2.2.3 Marketing Experience

Nivolumab monotherapy (Opdivo®) was first approved in July 2014 in Japan for unresectable melanoma (Nivolumab Investigator's Brochure, 2018). Since then, it has been approved in multiple countries, including the US, and has been approved for several other indications, including metastatic NSCLC, advanced RCC, cHL, SCCHN, urothelial carcinoma, HCC, RCC, and adjuvant treatment of melanoma. Nivolumab is also approved in combination with ipilimumab for unresectable or metastatic melanoma in multiple countries, including the US, and for previously untreated advanced RCC in the US. Qualitative and quantitative safety data has been consistent with the established safety profile as observed in clinical trials. No new safety concerns have been identified based on global post-marketing reports.

2.2.3 Ipilimumab

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4, Yervoy®) is an Ig-G1κ HuMAb specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T-cells (Ipilimumab Investigator's Brochure, 2018). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and inhibits its interaction with ligands on APCs. Blockade of CTLA-4 has been shown to augment T cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

2.2.3.1 Nonclinical Development of Ipilimumab

Ipilimumab has specificity and high affinity for human CTLA-4 (Ipilimumab Investigator's Brochure, 2018). The calculated dissociation constant value (K_D) from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15 ng/mL, while saturation was observed at approximately 0.1 mcg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of the CTLA-4 ligands B7-1 and B7-2 to human CTLA-4 at concentrations higher than 6 mcg/mL and 1 mcg/mL, respectively.

In vivo, blockade of CTLA-4, utilizing anti-CTLA-4 mAb, induced regression of established tumors and enhanced antitumor immune responses in several murine tumor models (Ipilimumab Investigator's Brochure, 2018). Blockade of CTLA-4-mediated signals is effective in inducing rejection of immunogenic cancers in mice. Moreover, when anti-CTLA-4 mAb is used in conjunction with granulocyte macrophage-colony stimulating factor (GM-CSF)-secreting tumor vaccines, poorly immunogenic cancers in mice are rejected. These findings suggest that CTLA-4 blockade, alone or in combination with antigenic stimulation and other immune modulating agents can induce a potent antitumor response. Complete information on pre-clinical studies can be found in the ipilimumab Investigator's Brochure (2018).

2.2.3.2 Clinical Development of Ipilimumab

Bristol-Myers Squibb (BMS) and Medarex (acquired by BMS in September 2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing >22,571 patients in several cancer types in completed and ongoing studies, including a compassionate use program (Ipilimumab Investigator Brochure, 2018). The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

CTEP's clinical development of ipilimumab focuses on cervical, GI, ovarian, prostate cancer, chronic lymphocytic leukemia, head and neck squamous cell carcinoma, solid tumors, Hodgkin and non-Hodgkin lymphomas, melanoma, and myelodysplastic syndrome. While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for each of the single agents.

2.2.3.2.1 Clinical Pharmacokinetics

The PK of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks (q3w) for four doses (Ipilimumab Investigator's Brochure, 2018). C_{max}, trough concentration (C_{min}), and AUC of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered q3w, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The mean terminal half-life was 14.7 days, systemic clearance (CL) was 15.3 mL/h, and the volume of distribution at steady-state (V_{ss}) was 7.21 L. The mean ipilimumab C_{min} achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL.

2.2.3.2.2 Safety

The immune-based mechanism of action is reflected in the safety profile of ipilimumab (Ipilimumab Investigator's Brochure, 2018). The most common treatment-related AEs are inflammatory in nature, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. Such immunological safety events are described as immune-related adverse events (irAEs) or immune mediated adverse reactions (imARs). The irAEs are described as AEs of unknown etiology, which were consistent with an immune phenomenon and considered causally related to drug exposure by the investigators. The irAEs primarily involve the GI tract and skin. Immune-related AEs in the liver were also observed, particularly in patients receiving 10 mg/kg. Endocrinopathy and neuropathy were important irAEs that were observed less frequently. The imARs were adjudicated in a blinded fashion based on sponsor-physician data review to exclude noninflammatory etiologies, such as infection or tumor progression, and to consider available evidence of inflammation, such as tumor biopsies or responsiveness to steroids, in an effort to

determine whether specific AEs or abnormal hepatic laboratory values were likely to be immune mediated and associated with ipilimumab treatment.

2.2.3.2.3 Efficacy

In melanoma, four completed phase 3 studies (MDX010-20, CA184024, CA184029, and CA184169) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma, in previously untreated advanced melanoma, and in adjuvant melanoma (Ipilimumab Investigator's Brochure, 2018).

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients (Ipilimumab Investigator's Brochure, 2018). Ipilimumab induces an immunologic response, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some patients) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination, and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in patients who are not experiencing rapid clinical deterioration, confirmation of progression is recommended (at the investigator's discretion) to better understand the prognosis, as well as to avoid unnecessarily initiating potentially toxic alternative therapies in patients who might be benefiting from treatment. Immune-related response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies. In metastatic diseases, stabilization is more common than response, and in some instances is associated with a slow, steady decline in tumor burden over many months, sometimes improving to PRs and/or CRs. Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to improvements in OS.

Available preclinical data support the combinations of nivolumab and ipilimumab (Curran *et al.*, 2010). The combination of ipilimumab with nivolumab has been reported to result in improved responses in advanced melanoma, including decreased time to response, increased number of responses, improved depth and duration of responses, and increased PFS and OS compared to single agent ipilimumab (Wolchok *et al.*, 2013).

2.2.3.3 Marketing Experience

Ipilimumab monotherapy (Yervoy®) was approved in the US in March 2011 for the treatment of advanced melanoma (Ipilimumab Investigator's Brochure, 2018). Ipilimumab has demonstrated long-term OS benefit extending beyond 5 years in both previously treated and untreated patients with metastatic melanoma. Ipilimumab continues to demonstrate an overall favorable benefit-risk profile. Based on review of nonclinical, clinical, and post-marketing data, there has been no change in the effectiveness or safety of ipilimumab for the approved indications. The totality of

data continues to support a significant clinical benefit for patients receiving ipilimumab with various other types of concomitant cancer stimulatory therapies.

2.3 Rationale

There is currently no FDA-approved agent in the 2nd-line setting for patients with RAI-refractory DTC. In an attempt to fill this gap, our group recently completed a prospective, open label phase 2 study of XL184 (cabozantinib) in patients with RAI-refractory DTC who progressed after VEGFR-targeted therapy (Cabanillas *et al.*, 2017). This study showed 40% partial response rates to XL184 (cabozantinib) and the median PFS was 12.7 months. Data from this trial (NCI trial 9312, NCT01811212) provides support for off-label use of XL184 (cabozantinib) as salvage therapy. In this proposal, we aim to build upon the success of single agent XL184 (cabozantinib) seen in this trial.

2.3.1 Rationale for combining XL184 (cabozantinib) with Immunotherapy

Tumor-involved lymph nodes (TILN) in PTC are enriched with PD-1+ T Cells and regulatory CD4+ T cells (T_{regs}), alluding to the role of immunosuppression in patients with metastatic PTC (French *et al.*, 2012). The frequency of PD-1+ T cells has been shown to be significantly greater in tumors with extranodal invasion compared with those without, suggesting an association between an abundance of PD-1+ T cells in TILN and an aggressive PTC phenotype. Similarly, T_{reg} levels are significantly higher in TILN compared with uninvolved lymph nodes (UILN), with an even greater frequency in patients with recurrent tumor. Upregulation of B7H1 mRNA and B7H1 protein has been noted in DTC, in contrast to low levels in benign lesions (Cunha *et al.*, 2013). Patients with Stage II-IV disease had significantly higher B7H1 mRNA levels compared with those with stage I cancers. High B7H1 protein was also significantly associated with the presence of CD4C, CD8C, CD20C, and FoxP3C lymphocytes, tumor-associated macrophages, and MDSCs. In a tissue banking study investigating the role of immunomodulation in thyroid cancer, PD-1 and PD-L1 expression were noted in 20% and 64% of DTC samples respectively (Bastman *et al.*, 2016). FoxP3, PD-1 CD8, and PD-1 CD4 T cells were all noted to be abundant in DTC. PTC cells have also been shown to have low expression of MHC class I molecules HLA-A, B, and C, and high expressions of immunosuppressive immune checkpoint PD-L1 and CD73 (Sakakura *et al.*, 2016). Thus, immune evasion by tumors appears to play a vital role in the pathogenesis of DTC, making immune checkpoint inhibitors an attractive treatment option.

Pembrolizumab, an anti-PD-1 antibody, is currently being studied in a phase 1b study (KEYNOTE 028, NCT02054806) in patients with PD-L1+ (PD-L1 ≥1%) select advanced solid tumors, including a cohort of patients with advanced PTC and FTC (Mehnert *et al.*, 2016). After a median follow-up of 73.5 weeks, 12 of 22 patients (54.5%) enrolled in the thyroid cohort had stable disease (SD) and 2 (9.1%) had PRs. In this study, 50% of patients had received ≥2 prior therapies for metastatic disease. The 6-month OS and PFS rates were 100% and 58.7% respectively. Treatment related adverse events were noted in 18/22 (81.8%) patients, with diarrhea and fatigue occurring in ≥15%. Results of the recently completed phase 2 KEYNOTE-158 trial (NCT02628067) of single-agent pembrolizumab of patients with advanced solid tumors, including thyroid cancers, are still pending.

2.3.2 Rationale for the proposed therapeutic agents

2.3.2.1 XL184 (cabozantinib)

XL184 (cabozantinib) is an oral multi-kinase inhibitor (MKI) with potent activity against MET, VEGFR2, and RET kinase. Phase 1-3 clinical trials of XL184 (cabozantinib) have been conducted in a variety of solid tumors, including thyroid cancers, and has been shown to have an acceptable toxicity profile. Impressively high response rates were noted in a multicenter, NCI and International Thyroid Oncology Group (ITOG)-funded prospective phase 2 study of XL184 (cabozantinib) in patients with RAI refractory DTC, who progressed on prior VEGFR- targeted therapy (NCI trial 9312, NCT01811212) (Cabanillas *et al.*, 2017). Of 25 total patients, 10 (40%) had PRs and 13 (52%) had SD. Most patients in this study (21 of 25) had received only one prior VEGFR-targeted therapy. Median PFS and OS were 12.7 months and 34.7 months, respectively. XL184 (cabozantinib) is therefore a promising treatment option in these patients.

In vitro experiments with MC38-CEA, a murine colon carcinoma cell line, showed that XL184 (cabozantinib) upregulated tumor MHC-1 expression; increased expression of several markers mediating T cell responses, including ICAM-1, Fas, and calreticulin; increased tumor susceptibility to cytotoxic T cell mediated destruction; and increased the percentage of CD8+ T cells in the peripheral immune environment while reducing the percentage of T_{regs} and MDSCs (Kwilas *et al.*, 2014). In combination with a poxvirus-based cancer vaccine, XL184 (cabozantinib) nullified the effect of T_{regs}, while increasing the production of IFN-γ and tumor necrosis factor alpha (TNF-α). Combination therapy also resulted in significantly increased CD3+ and CD8+ T cells. When compared to XL184 (cabozantinib) or cancer vaccine monotherapy, combination therapy resulted in significantly lower MDSC and tumor-associated macrophage infiltration, and a significantly lower rate of tumor growth, with half of the mice showing durable treatment responses.

2.3.2.2 Nivolumab and Ipilimumab

Nivolumab is an anti-PD-1 monoclonal antibody that is efficacious in the treatment of several malignancies including metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma (RCC), classical Hodgkin lymphoma, SCCHN, urothelial carcinoma, and HCC (Nivolumab Investigator's Brochure).

Ipilimumab is a human anti-CTLA4 monoclonal antibody that has shown encouraging clinical efficacy and an acceptable safety profile in cutaneous melanoma (Ipilimumab Investigator's Brochure, 2018). It is currently FDA-approved for use in patients with metastatic melanoma and for adjuvant treatment in patients with high risk cutaneous melanoma.

The synergistic effects of combination antibody blockade have been clinically validated. In a phase 2 study of patients with untreated metastatic melanoma, the objective response rate and PFS were significantly greater in those receiving ipilimumab plus nivolumab when compared to ipilimumab alone (P<0.001) (Postow *et al.*, 2015). The combination had an acceptable safety profile, with drug-related grade 3 or 4 events reported in 54% of patient on combination therapy

compared with 24% of those on monotherapy. In a subsequent phase 3 study of patients with advanced melanoma comparing efficacy of ipilimumab plus nivolumab *vs.* nivolumab *vs.* ipilimumab, the ORR was 57.6% with combination therapy, 43.7% with nivolumab alone, and 19% with ipilimumab alone (Larkin *et al.*, 2015). PFS of patients on ipilimumab plus nivolumab therapy was 11.5 months *vs.* 6.9 months with nivolumab alone *vs.* 2.9 months with ipilimumab alone. The impressively greater efficacy of ipilimumab plus nivolumab compared to either agent alone led to the FDA approval of the combination for the treatment of unresectable or metastatic melanoma (Nivolumab Investigator's Brochure, 2018). Combination therapy is also approved for advanced RCC.

2.3.3 Encouraging results of CaboNivoIpi in early-phase clinical trials

The safety and efficacy of XL184 (cabozantinib) once daily (QD) plus nivolumab every 2 weeks and XL184 (cabozantinib) QD plus nivolumab and ipilimumab every 3 weeks for 4 doses followed by XL184 (cabozantinib) QD plus nivolumab every 2 weeks was evaluated in a phase 1 study of patients with metastatic urothelial and other genitourinary (GU) tumors (Apolo *et al.*, 2017). In patients receiving the triplet combination therapy, grade 3 treatment-related AEs were hypophosphatemia (13%), lipase increased (13%), fatigue (6%), alanine aminotransferase (ALT) increased (6%), hypertension (6%), and colitis (6%). There were no dose-limiting toxicities (DLTs) or grade 5 AEs. Of the 38 patients evaluable for response (across both cohorts), ORR was 32% (12/38) with 1 CRs and 11 PRs and 20 patients with SD (58%).

2.3.4 Rationale for the proposed doses

The recommended dose for CaboNivoIpi in the above phase 1 study in patients with metastatic GU solid tumors was XL184 (cabozantinib) 40 mg/day, nivolumab 3 mg/kg, and ipilimumab 1 mg/kg every 3 weeks for 4 doses, followed by XL184 (cabozantinib) 40 mg/day plus Nivolumab 3 mg/kg every 2 weeks (Apolo *et al.*, 2017). Continuous dosing of nivolumab 3 mg/kg every 2 weeks combined with ipilimumab 1 mg/kg every 6 weeks has been shown to be better tolerated when compared to the above schedule, while maintaining a similar level of efficacy in patients with NSCLC (Hellmann *et al.*, 2017). The equivalent efficacy and safety of weight-based (3 mg/kg every 2 weeks) and flat dosing (240 mg every 2 weeks) of Nivolumab (Zhao *et al.*, 2017), led to the recent FDA approval of modification of the recommended dosage regimen of Nivolumab from 3 mg/kg to 240 mg IV every 2 weeks in patients with metastatic melanoma, RCC, or NSCLC.

2.3.5 Summary

We propose the use of CaboNivoIpi in patients with RAI-refractory DTC who have progressed on prior VEGFR therapy based on following:

1. High PR rates with XL184 (cabozantinib) alone in patients with advanced RAI refractory DTC whose disease progressed on prior VEGFR therapy (Cabanillas *et al.*, 2017);
2. Encouraging data on the efficacy and safety of the combination of CaboNivoIpi in metastatic urothelial and GU tumors (Apolo *et al.*, 2017);

3. Encouraging phase 1b data on the efficacy and safety of the immune checkpoint inhibitor, pembrolizumab, in patients with metastatic PTC and FTC (Mehnert *et al.*, 2016).

2.4 Correlative Studies Background

2.3.6 Tumor genetics

Cabozantinib is an oral, multi-kinase inhibitor with activity against MET, VEGFR2, and RET kinases. Close to 70% of DTC have somatic genomic alterations in RET, NTRK1, BRAF, or RAS. These are mutually exclusive activating mutations that drive thyroid tumorigenesis (Kondo *et al.*, 2006). Activation of the RAS/RAF signaling pathway has been shown to stimulate angiogenic protein production. However, whether somatic genomic alterations predict response to XL184 (cabozantinib), an anti-angiogenic TKI, in combination with nivolumab and ipilimumab is unclear. In a phase 2 study by our group evaluating the efficacy of XL184 (cabozantinib) in patients with DTC, patients with NRAS mutations and a patient with mutated KRAS had significant treatment response (Cabanillas et al., 2017). However, comprehensive genomic profiles were not obtained in this study. In a phase 2 study of lenvatinib (a VEGFR inhibitor) in DTC, a combination of RAS and BRAF mutation in archival tissue and baseline circulating cytokine angiogenic factor correlated with lenvatinib treatment response (Ball et al., 2012). In a subsequent phase 3 study evaluating the efficacy of lenvatinib in RAI-refractory DTC, patients with BRAF mutated PTC had longer PFS compared to those without, indicating that BRAF mutation status may have prognostic value (Tahara et al., 2017). However, neither BRAF nor RAS mutations were predictive of response to lenvatinib. We hypothesize that the genetic make-up of tumors might predict response to CaboNivoIpi in patients with DTC.

2.3.7 Immunological subsets

The extent of tumor infiltration by lymphocytes have been associated with clinical outcomes in several cancer types (Galon *et al.*, 2006; Zhang *et al.*, 2003). For thyroid cancers, lymphocyte density within the tumor at surgical resection correlates with better OS, reduced tumor size, increased disease-free survival (DFS) and lower rate of tumor recurrence (Cunha *et al.*, 2012; Matsubayashi *et al.*, 1995). These findings suggest that a T cell-mediated immune response has the capacity to modulate outcomes in thyroid cancers and augmenting this immune response may provide clinical benefits. The preliminary results from an early-phase clinical trial of pembrolizumab in patients with advanced thyroid cancers, in which a substantial proportion of patients derived clinical benefit from the treatment, support these observations (Mehnert *et al.*, 2016). In addition, immune checkpoint inhibitors have been shown to have an anti-tumor effect through inducing the proliferation of pre-existing T cells (Tumeh *et al.*, 2014; Zitvogel *et al.*, 2013).

There is emerging evidence that the clinical benefits of conventional chemotherapies and kinase inhibitors may be partly mediated by their impact on the immune system (Forde *et al.*, 2018). Imatinib, a multi-targeted kinase inhibitor, was shown to induce tumor-specific T cells in patients with chronic myeloid leukemia (CML) and GI stromal tumors (GIST) (Chen *et al.*, 2008; Larmonier *et al.*, 2008). In a phase 2 study of XL184 (cabozantinib) in advanced/metastatic urothelial cancer (NCT01688999), patients with low levels of T_{regs} at

baseline had better treatment response, PFS, and OS compared to those with high baseline levels (Apolo *et al.*, 2014). The levels of peripheral blood T_{regs} decreased (P=0.015) and PD-1 expression in T_{regs} increased (P=0.011) following 2 cycles of treatment with XL184 (cabozantinib). A change in PD-1 levels below median, and a decrease in CD40 expression in MDSCs following treatment were both associated with improved PFS. These results suggest an immunomodulatory role of XL184 (cabozantinib) leading to improved outcomes. We therefore propose to study the effect of XL184 (cabozantinib) in combination with ipilimumab and nivolumab on the tumor microenvironment (tumor infiltrating lymphocytes [TILs]) and peripheral immune subsets. We hypothesize that CaboNivoIpi combination therapy will synergistically induce and/or augment tumor-targeting T cells in order to improve overall clinical outcomes for patients with DTC. We expect that XL184 (cabozantinib) will initially induce immunogenic cell death which will bolster anti-tumor T cell response and the subsequent addition of nivolumab and ipilimumab 2 weeks later will further augment this response.

2.3.8 T cell receptor sequencing

We propose to characterize the longitudinal dynamics of tumor-associated T cells using next generation TCR sequencing and single cell sequencing. This will help define the capacity of XL184 (cabozantinib) to induce immunogenic cell death and for nivolumab and ipilimumab to further augment this response. The development of TCR sequencing has allowed identification and tracking of individual T cell clones (Savas *et al.*, 2018). This is now widely applied in the development of predictive and correlative biomarker of response to immune checkpoint inhibitors in general (Forde *et al.*, 2018; Tumeh *et al.*, 2014). We also plan to define the molecular characteristics of individual T cell clones through single cell transcriptomics (Savas *et al.*, 2018). Such in-depth study will allow us to identify the factors that determine response to these agents, define the mechanism through which they eradicate thyroid cancers, and also establish synergism between XL184 (cabozantinib) and immune checkpoint inhibitors.

2.3.9 PD-1/PD-L1 testing

PD-L1 overexpression has been shown to predict treatment response to immune checkpoint inhibitors in multiple tumor types including but not limited to melanoma, NSCLC, ovarian cancer, and RCC (Meng *et al.*, 2015). In a sensitivity analysis of twenty phase 1-3 clinical trials evaluating the role of nivolumab, pembrolizumab, and atezolizumab in patients with melanoma, NSCLC, and genitourinary cancer, overall response rates were significantly higher in the PD-L1-positive patients, compared to those whose tumors were PD-L1-negative (Carbognin *et al.*, 2015). When stratified based on treatment received, patients with PD-L1-positive tumors who received pembrolizumab and nivolumab had significantly higher response rates compared to those with PD-L1-negative tumors. This difference was not seen in patients who received atezolizumab, suggesting that PD-L1 expression may be a predictive biomarker in patients who receive anti-PD-1 therapy. Tissue banking data have revealed that 50% and 64% of DTC samples express PD-1 and PD-L1, respectively (Bastman *et al.*, 2016). We plan to perform IHC for expression of PD-1 and PD-L1 in tissue. Given that PD-1/PD-L1 expression is a dynamic process, and is affected by immune checkpoint inhibitor therapy (Vilain *et al.*, 2017), we will evaluate PD-1 and PD-L1 using IHC on fresh tumor tissue obtained at baseline and at Cycle 3

Day 1. In patients who refuse baseline biopsies, archival tissue will be used for evaluation of PD-1/PD-L1 status at baseline.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed PTC, FTC, or HTC. Follicular variant of PTC or any of the above mixed histology will be allowed, as well as tall cell, insular, or poorly-differentiated thyroid cancers. Patients with ATC or MTC are not eligible.

3.1.2 Patients must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

3.1.3 Patients must have RAI-refractory/resistant disease as defined by one or more of the following criteria:

a. One or more measurable lesions that do not demonstrate RAI uptake,
b. Progressive disease (PD) (new lesion or progression of previously known lesions), as defined by RECIST v1.1, within 12 months of prior RAI therapy,
c. One or more measurable lesion present after cumulative RAI dose of >600 mCi, or
d. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan-positive disease (SUV ≥5 in tumor lesion).

3.1.4 The patient's disease must have progressed on one line of VEGFR-targeted therapy (including, but not limited to, sorafenib, sunitinib, vandetanib, pazopanib, or lenvatinib, *etc.*) as defined by PD per RECIST v1.1 while receiving VEGFR-targeted therapy. Patients who have received more than one line of prior VEGFR-targeted therapy will not be eligible.

Prior external beam radiation to extra-osseous disease, systemic cytotoxic chemotherapy or BRAF- or non-VEGFR-targeted therapies will be allowed, provided that >4 weeks has elapsed since receiving prior treatment. Radiation to bone metastases is allowed up to 2 weeks prior to initiation of study treatment.

3.1.5 Patients must be ≥18 years of age. Because no dosing or adverse event data are currently available on the use of XL184 (cabozantinib), nivolumab, or ipilimumab in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.1.6 Patients must have ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.7 Patients must have recovered to baseline or ≤ Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 1 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

3.1.8 Patients must have adequate organ and marrow function as defined below:

– absolute neutrophils	≥1,500/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥9 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN); ≤3.0 × ULN for patients with Gilbert's syndrome
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional ULN
– alkaline phosphatase	≤3.0 × institutional ULN; ≤5.0 × ULN with documented bone metastases
– creatinine	≤1.5× ULN OR
– creatinine clearance (CrCl)	≥50 mL/min (if using the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

– serum albumin	≥2.8 g/dL
– lipase	<2.0 × ULN and no radiologic or clinical evidence of pancreatitis
– urine protein/creatinine ratio (UPCR)	≤1 mg/mg
– serum phosphorus, calcium, magnesium, and potassium	within institutional normal limits
– prothrombin time (PT)/International Normalized Ratio (INR) and partial thromboplastin time (PTT) test	<1.3 × ULN

3.1.9 Patients with a history of human immunodeficiency virus (HIV) infection must be on an effective anti-retroviral regimen utilizing agents that do not strongly induce or inhibit cytochrome P450 (CYP) 3A4, and must have an undetectable viral load measured within 6 months prior to study registration.

3.1.10 Patients with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on suppressive therapy, if indicated.

3.1.11 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load.

3.1.12 The effects of XL184 (cabozantinib), nivolumab, and ipilimumab on the developing human fetus are unknown. For this reason, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP should use an adequate method to avoid pregnancy for 5 months after the last dose of study therapy. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity: 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of study therapy. Women must not be breastfeeding. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of <1% per year. Men who receive study therapy and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of study therapy. Women who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

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 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 <40 mIU/mL.

WOCBP and men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 5 and 7 months, respectively, after the last dose of study therapy. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) must inform the treating physician immediately.

3.1.13 Patients must be able to swallow tablets

3.1.14 Patients must be able to understand be willing to sign a written informed consent document.

3.1.15 Patients with impaired decision-making capacity (IDMC) will be eligible if they have a legally authorized representative (LAR) or caregiver available to assist them.

3.2 Exclusion Criteria

3.2.1 Patients must not have had prior treatment with XL184 (cabozantinib), any MET-targeting TKI, or any MET-targeting monoclonal antibody (MetMAb), such as onartuzumab.

3.2.2 Patients must not have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways.

3.2.3 Patients must not have a tumor invading or encasing any major blood vessels, and must not have 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).

3.2.4 Patients must not have a diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy. Adjuvant hormonal therapy for history of prostate or breast cancer is allowed.

3.2.5 Patients must not have received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (*e.g.*, cytokines or antibodies) within 4 weeks, or nitrosoureas/ mitomycin C within 6 weeks, before the first dose of study treatment. Patients may continue on bone-modifying agents (denosumab or bisphosphonates) with caution.

3.2.6 Patients must not have received radiation therapy:

- to the thoracic cavity, abdomen, or pelvis within 4 weeks before the first dose of study treatment;
- to bone metastases within 14 days before the first dose of study treatment;
- to any other sites within 4 weeks before the first dose of study treatment.

3.2.7 Patients must not have clinically relevant, ongoing complications from prior radiation therapy. Palliative (limited-field) radiation therapy is permitted as long as the patient does not have disease progression according to RECIST v 1.1.

3.2.8 Patients must not have received any type of small molecule kinase inhibitor (including investigational kinase inhibitors) within 4 weeks before the first dose of study treatment.

3.2.9 Patients must not have received any other type of investigational agent within 4 weeks before the first dose of study treatment.

3.2.10 Patients must not have a corrected QT interval calculated by the Fridericia formula (QTcF) >500 msec by electrocardiogram (EKG) within 28 days before the first dose of study treatment.

Note: If a single EKG shows a QTcF with an absolute value >500 msec, two additional EKGs at intervals of approximately 3 min must be performed within 30 min after the initial EKG, and the average of these three consecutive results for QTcF will be used to determine eligibility.

3.2.11 Patients should not have known, untreated brain metastases or leptomeningeal metastases because of poor prognosis and concerns that progressive neurologic dysfunction could confound the evaluation of neurologic and other adverse events. However, patients will be eligible if metastases have been treated, and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment for metastases is complete and within 28 days prior to the first dose of study treatment.

3.2.12 Patients must not require concomitant treatment with oral anticoagulants (*e.g.*, warfarin, direct thrombin, and Factor Xa inhibitors) or platelet inhibitors (*e.g.*, clopidogrel). The following anticoagulants are allowed:

- Low-dose aspirin for cardioprotection (per local applicable guidelines),
- Low-dose low molecular weight heparins (LMWH),
- Therapeutic doses of LMWH are allowed in patients without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

3.2.13 Patients must not require systemic corticosteroids treatment (≥10 mg/day prednisone equivalents) or other immunosuppressive medications within 14 days prior to study drug administration. Inhaled or topical steroids and adrenal replacement doses <10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if ≥10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted, as is steroid pre-medication for contrast allergy.

3.2.14 Patients must not have a history of severe hypersensitivity reactions to any monoclonal antibodies.

3.2.15 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in study.

3.2.16 Patients must not require concomitant treatment with strong CYP3A4 inducers (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, or St. John's Wort). Because 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/table.aspx. Medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, patients 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.

Appendix B contains a patient clinical trial wallet card that can be given to patients.

3.2.17 Patients must not have uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
  - Congestive heart failure New York Heart Association (NYHA) Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
  - Uncontrolled hypertension defined as sustained blood pressure (BP) >140 mm Hg systolic or >90 mm Hg diastolic despite optimal antihypertensive treatment within seven days prior to the first dose of study treatment.
  - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (*e.g.*, deep venous thrombosis [DVT], pulmonary embolism [PE]) within 6 months before first dose.
- GI disorders including those associated with a high risk of perforation or fistula formation:
  - The patient has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (*e.g.*, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
  - Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Complete healing of an intra-abdominal abscess must be confirmed before first dose.
- Clinically significant hematuria, hematemesis, or hemoptysis or other history of significant bleeding (*e.g.*, pulmonary hemorrhage) within 12 weeks before first dose.
- Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
- Lesions invading or encasing any major blood vessels.
- Other clinically significant disorders that would preclude safe study participation.
  - Serious non-healing wound/ulcer/bone fracture.
  - Uncompensated/symptomatic hypothyroidism.
  - Moderate to severe hepatic impairment (Child-Pugh B or C).

3.2.18 Patients must not have had major surgery (*e.g.*, GI surgery or removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment and from minor surgery (*e.g.*, simple excision or tooth extraction) at least 10 days before the first dose. Patients with clinically relevant ongoing complications from prior surgery are not eligible.

3.2.19 Pregnant women are excluded from this study because XL184 (cabozantinib) has the potential for teratogenic or abortifacient effects, and the effects of nivolumab and ipilimumab on the developing fetus are not well known. Because there is an unknown

but potential risk for AEs in nursing infants secondary to treatment of the mother, breastfeeding must be discontinued if the mother is treated with XL184 (cabozantinib), nivolumab, or ipilimumab.

3.2.20 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including high dose systemic corticosteroids, should be excluded. These include but are not limited to: immune-related neurologic disease, such as multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, or myasthenia gravis; systemic autoimmune disease such as Systemic Lupus Erythematosus (SLE), connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, or autoimmune hepatitis. Patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, type I diabetes mellitus (DM), or endocrine deficiencies (*e.g.*, thyroiditis) managed with replacement hormones, including physiologic corticosteroids, are eligible.

Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication, and patients with positive serology, (*e.g.*, antinuclear antibodies (ANA) or anti-thyroid antibodies) should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.3 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 patients 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.

Please refer to the table in Section 9.2 for the planned distribution of patients by sex/gender, race, and ethnicity.

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 at 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 Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*,

Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. 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).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-OH007, and protocol number 10240,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For 10240 Site Registration

- Site Initiation Teleconference
- Specimen 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.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

4.2.4 Checking Site Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. 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

Special Instructions for Patient Enrollment

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

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- 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.

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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 Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.3.3 Patient Enrollment Instructions

Upon enrolling a patient, IWRS will communicate with OPEN, assigning three separate and unique identification numbers to the patient, a Universal Patient ID (UPID), an Intrinsic ID, and a Treatment Patient ID. The UPID and Intrinsic ID are both associated with the patient and used each and every time the patient engages with the biomarker portion of this protocol (see Section 5). Neither of these IDs contain any information or link to this treatment protocol. IWRS will maintain an association between the UPID for any treatment protocols the patient participates in, thereby allowing analysis of biomarker results with the clinical data. The Intrinsic ID is needed by the Biorepository to maintain quality control of positively identifying specimens for association with a particular patient.

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) and the IWRS-assigned UPID for this trial.

Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 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 canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

All correlative studies will only be done in Stage 2 (14 patients only), after the interim efficacy endpoint is met.

Time Point	Specimen	Send Specimens To:
Archival		
	• Submit: • 1 H&E stained slide • 8-10 positive charged slides (4 micron) (baked) • 30-50 unstained, positive charged, air-dried slides (10 micron), numbered sequentially (air-dried) *And* • 4 unstained positive charged slides (4 micron) (baked) If all of above slides are not available, please submit the number of slides that are available.	ETCTN Biorepository
Baseline (Day -14)		
	• 2 cores in formalin (optional) • 8 mL whole blood in CPT tube with sodium citrate for T cell clonality assays	ETCTN Biorepository
	• 10 mL whole blood in EDTA tubes (purple top) for PBMC and MDSC analysis	OSU Flow Cytometry Lab

Time Point	Specimen	Send Specimens To:
Cycle 1, Day 1		
	• 8 mL whole blood in CPT tube with sodium citrate for T cell clonality assays • 10 mL whole blood in EDTA tubes (purple top) for PBMC and MDSC analysis	ETCTN Biorepository
	• 10 mL whole blood in EDTA tubes (purple top) for PBMC and MDSC analysis	OSU Flow Cytometry Lab
Cycle 3, Day 1		
	• 2 cores in formalin (optional) • 8 mL whole blood in CPT tube with sodium citrate for T cell clonality assays	ETCTN Biorepository
	• 10 mL whole blood in EDTA tubes (purple top) for PBMC and MDSC analysis	OSU Flow Cytometry Lab
At Progression		
	• 8 mL whole blood in CPT tube with sodium citrate for T cell clonality assays	ETCTN Biorepository
	• 10 mL whole blood in EDTA tubes (purple top) for PBMC and MDSC analysis •	OSU Flow Cytometry Lab

[1]*For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51).*

[2]*For new biopsies, the Tissue Biopsy Verification Form (Appendix E) and a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the ETCTN Biorepository. When completed, upload the corresponding pathology report to Rave and send a copy to the ETCTN Biorepository.*

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Collection and Shipping Kits

Tissue collection kits, EDTA tubes (purple top), CPT tubes with sodium citrate, and associated shipping materials should be obtained from commercial sources.

Kits for the collection and shipment of formalin-fixed tissue to the ETCTN Biorepository can be ordered online via the Kit Management system: (https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Blood collection supplies, including EDTA tubes (purple top), CPT tubes with sodium citrate, and associated shipping materials should be obtained from commercial sources

5.2.2 Scheduling of Specimen Collections

- Baseline (Day -14) samples (blood and tumor tissue) should be collected prior to starting XL184 (cabozantinib) therapy.
  - Tumor biopsy samples may be collected up to five days before the specified timepoint, but should be collected at least 2 days (48 hours) prior to starting XL184 (cabozantinib) therapy.
  - Blood samples may be collected up to three days before the specified timepoint.

- Cycle 1, Day 1 blood samples:
  - Samples should be collected prior to beginning nivolumab and ipilimumab therapy, and may be collected up to three days before the specified timepoint.
- Cycle 3, Day 1 tumor biopsy and blood samples:
  - Tumor biopsy samples may be collected ±5 days from the specified timepoint.
  - Blood samples may be collected ±3 days from the specified timepoint.
  - XL184 (cabozantinib) should be held starting 2 days (48 hours) prior to the biopsy procedure until 2 days (48 hours) after the biopsy procedure.

- Blood samples collected at progression may be collected ±3 days from the specified timepoint.

Please adhere to the following guidelines when scheduling procedures to collect tissue:
- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day as the collection.
- Fresh blood should be shipped for overnight delivery on the same day as collection (please refer to shipping-day preference instructions in Section 5.5).

5.3 Specimen Tracking System Instructions

It is required that all samples submitted on this trial be entered and tracked using the ETCTN Rave 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 the analysis labs. 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 assay result reporting delays. Any case reimbursements associated with sample submissions will not be credited if samples are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

A user manual is available at

http://theradex.com/downloads/ETCTN_Specimen_Tracking_User_Guide.pdf.

A shipping manifest must be included with all sample submissions.

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

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 **Error! Reference source not found.**.
- 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. **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.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

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

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)

- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date *and time* (to be added by hand)

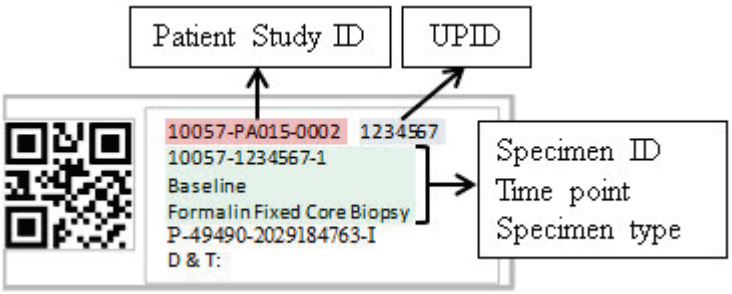
5.3.2.2 Tissue Specimen Labels

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.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary or M for metastatic)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date *and time* (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery 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 31-Aug-2018; 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.

5.3.3 Overview of Process at Treating Site

5.3.3.1 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 setup 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.

5.3.3.2 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 clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and 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 *and time* on each label. After collection, store labeled specimens as described in Section 5.4.
- Apply an extra specimen label to <u>*each*</u> report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) 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 protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates (such as collection date), 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 email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 Biopsy Collection Procedure

5.4.1.1 Core Needle Biopsy

XL184 (cabozantinib) should be held starting 2 days (48 hours) prior to the biopsy procedure, and may be resumed 2 days (48 hours) following the procedure, unless there is evidence of biopsy wound-related complications or incomplete wound healing. Due to the risk of perforation and fistula with XL184 (cabozantinib), transesophageal and other transluminal biopsies should not be performed, and biopsies should not be performed in areas of prior fistula formation, surgery, or radiation.

For the collection of biopsy specimens, core needle biopsy is the required technique. It is preferred that two core biopsies, 16-18 gauge in diameter and at least 1 cm in length are obtained and shipped in formalin on the same day as collection to the ETCTN Biorepository (see Section 5.5 below). Specimens should be placed immediately into buffered formalin in a specimen collection container.

Core biopsies at least 1 cm in length will be obtained through Interventional Radiology by a percutaneous approach using a 16-18-gauge needle. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy or endoscopic biopsy is

allowed if medically indicated and can be used for analysis. Depending on the lesion site, a CT guided biopsy may be performed. Biopsies will be sent for analyses as defined in the protocol.

5.4.2 Archival Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

Archival FFPE tumor tissue, if available from prior surgery or biopsy, will be collected (primary tumor or metastatic site; primary tumor is preferred)

- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3.

If an existing block cannot be submitted, the following are requested, if available:

- One hematoxylin and eosin (H&E) slide,
- Thirty to fifty 10-µm unstained air-dried positively charged slides

Section the slides sequentially, and number each section (e.g., H&E slide is 1, unstained slides 2 – 51).

See Section 5.3.1 for labeling instructions.

5.4.3 Formalin-Fixed Tumor Biopsies (RNAseq, TILs, T-cell clonality, PD-1/PD-L1 expression)

1. Label formalin-filled containers according to Section 5.3.1.
2. Obtain two 16-18-gauge core needle biopsy specimens and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a 10% neutral buffered formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and place the containers into the shipping kit. Keep tissue in formalin jars at room temperature until shipment.

5.4.4 Blood Collection

5.4.4.1 General Blood Collection Guidelines

Blood should be collected according to local institutional standards. When collecting multiple samples, CPT tubes should be filled before EDTA tubes.

1. Keep patient's arm in a downward position during the collection procedure.
2. Keep the tube upright at all times.
3. Remove tourniquet as soon as blood appears in tube, within 2 minutes of venipuncture.
4. Do not allow the tube contents to touch the stopper or the end of the needle during the collection procedure.
5. If no blood flows into the tube or if blood ceases to flow before an adequate sample (approximately 6-8 mL minimum) is collected:
   a. Confirm correct position of needle cannula in vein.
   b. If a multiple-sample needle is being used, remove the collection tube, and place a new tube into the holder.
   c. If the second tube does not draw, remove needle and discard in appropriate disposal device. DO NOT RESHIELD.

5.4.4.2 Collection of Blood in CPT Tubes with Sodium Citrate (T-cell clonality assay)

1. Label one CPT tube with sodium citrate according to Section 5.3.1. CPT tubes should be at room temperature prior to collection.
2. Collect 8-10 mL blood in the tube and gently invert tube to mix. However, if you are shipping during the winter, divide one tube into two tubes (*e.g.*, two 5 mL tubes from one 10 mL tube).
3. Ship on day of collection according to instructions below (Section 5.5).
4. Ship samples at ambient to the ETCTN Biorepository by Priority Overnight for next day delivery. Ideally, samples should be received within 24 hours of collection.

5.4.4.3 Collection of Blood in EDTA Tubes (PBMCs, Circulating MDSCs)

1. Label one EDTA (purple top) tube according to Section 5.3.1.
2. Collect 10 mL blood and gently invert tube to mix.
3. Ship on day of collection according to instructions below (Section 5.5).
4. Ship samples at ambient temperature to OSUMUC by Priority Overnight for next day guaranteed delivery. Ideally, samples should be received within 24 hours of collection.

5.5 Shipping Specimens from Clinical Sites to the ETCTN Biorepository

Core biopsies that are fixed in 10% neutral buffered formalin should be shipped at ambient temperature. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container and must not be frozen at any time prior to processing. During warm weather fresh blood should be shipped on a cold pack.

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.

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, 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. When available, upload the anatomic pathology report corresponding to that surgery.

5.5.1 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Fresh blood must be shipped on the day of collection and may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

FedEx Priority Overnight is strongly preferred to ensure prompt delivery.

5.5.1.1 Shipping Glass Slides

1. Before packaging slides, verify that slides are labeled according to Section 5.3.1.
2. Glass slides are to be placed in individual slots within slide boxes to ensure slides remain separated during shipment. Place tissue paper on top of the separated slides prior to closing the slide box to reduce slide movement within the box.
3. Slide boxes should then be placed in reinforced cardboard shipping boxes with appropriate packaging filler to minimize movement of the slide boxes within the shipping box.

5.5.1.2 Shipping Ambient Tissue (Formalin-Fixed Core Biopsies) in a Single Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to Section 5.3.1 and that the lids of all primary receptacles containing liquid are tightly sealed. The lids of formalin jars should be wrapped in parafilm. Absorbent material must be place around each formalin jar.
2. Place the formalin jars into resealable bags. Use a separate bag for each specimen type.
3. Place the formalin jars into the secondary pressure vessel and surround with bubble wrap. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
4. Place a copy of the shipping manifest and corresponding reports such as surgical or radiology reports into the kit chamber.
5. Place the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Attach an Exempt Human Specimen sticker to the side of the container.
8. Ship specimens to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.3 Shipping Fresh Blood-CPT Tubes Only

1. Before packaging specimens, verify that each specimen is labeled according to Section 5.3.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in resealable bags. Use a separate bag for each specimen type.
3. Place the specimen(s) and a copy of the shipping manifest into a shipping container provided by the institution. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
4. Attach a shipping label to the top of the shipping container.
5. Attach an Exempt Human Specimen sticker to the side of the container.
6. Ship specimens to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2 Shipping Address

All samples EXCEPT blood in EDTA tubes should be shipped to the address below. Ship specimen the same day as collection. Do not ship specimen the day before a holiday or on Friday.

ETCTN Biorepository
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
Phone: (614) 722-2865
Toll-free Phone: (800) 347-2486fhole
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

5.5.3 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

5.6 Shipping Specimens from Clinical Sites to the OSU Flow Cytometry Lab

5.6.1 Shipping Fresh Blood—EDTA tubes ONLY

1. Before packaging specimens, verify that each specimen is labeled according to Section 5.3.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in resealable bags. Use a separate bag for each specimen type.
3. Place the specimen(s) and a copy of the shipping manifest into a shipping container provided by the institution. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
4. Attach a shipping label to the top of the shipping container.
5. Attach an Exempt Human Specimen sticker to the side of the container.

6. Ship specimens to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

Please add shipping instructions as Section 5.6.2 and Contact Information as Section 5.6.3:

5.6.2 Shipping Address:

OSU Flow Cytometry Lab
410 W 10th Ave, 303 Doan
Attn: Rhonda Kitzler/Becky Pearson
Columbus, OH 43210

5.6.3 Contact Information for Assistance:

Rhonda L Kitzler Tel: 614-366-1597
Email: rhonda.kitzler@osumc.edu

Becky Pearson Tel: 614-366-7677
Email: rebecca.pearson@osumc.edu

As of August 20, 2021, stage 1 of the study reached its target accrual. Interim analysis for efficacy revealed that the study did not reach its pre-specified threshold for efficacy. The study therefore did not proceed to stage 2. As correlative studies were proposed to only be done in stage 2 of the study, no specimens for biomarkers were collected. In general, tumor genotyping (limited or broad) along with PD L1 and TMB testing is commonly performed at several institutions a patient's disease course to evaluate for actionable genomic alterations. For example, the presence of BRAF V600E mutation appears to portend an aggressive tumor biology and a poor prognosis [1]. In order to correlate study treatment response (RECIST v1.1) with tumor mutation status and PD L1 status, redacted tumor genotyping reports including tumor mutation burden and PDL1 status will be requested if these are available or will be available.

5.7 Biomarker Plan

Correlative studies will be done during Stage 2 of the study only. For patients who refuse biopsy, archival tissue will be used. The submission of archival tissue will be only requested from patients enrolled to Stage 2. Submission will be optional, but will be strongly encouraged.

Note:
Tumor genotyping will not be repeated for patients who have had genomic testing of their tumor performed prior to study enrollment.

PD-1/PD-L1 testing will not be repeated for patients from whom sufficient fresh tumor tissue cannot be collected on-study and who have had such analyses performed using archival tissue prior to study enrollment.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Point(s)*	Laboratory Performing Assay
1.	RNAseq	NGS	Integrated To evaluate changes in the tumor immune microenvironment caused by treatment with CaboNivoIpi.	O	• Fresh tumor core biopsy Day -14 (prior to stating study therapy – only fresh tumor tissue may be used) • C3D1 (after 12 weeks of CaboNivoIpi therapy) Time points are ± 5 days	NCLN Genomics Laboratory Lab PI: Mickey Williams, Ph.D. mickey.williams@nih.gov
2.	Tumor Infiltrating Lymphocytes (TILs)	IHC	Exploratory To correlate treatment response (RECIST v1.1) with frequency of TILs in biopsies taken pre- treatment and after 12 weeks of CaboNivoIpi therapy.	O	Fresh tumor core biopsy(8-10 FFPE tissue slides, 4-micron sections). Archival tissue will be used for patients who have insufficient fresh tissue or who refuse the biopsy (TIL Testing is first priority- 8-10 charged slides, 4-micron sections) • Day -14 (prior to starting study therapy) • C3D1 (after 12 weeks of CaboNivoIpi therapy) Time points are ±5 days	The Ohio State University Histology/IHC Lab Lab PI: Anil Parwani, M.D. Anil.Parwani@osumc.edu
3.	T-cell clonality	T cell receptor sequencing	Exploratory To evaluate the effect of CaboNivoIpi on TCR repertoire and to identify the frequency of shared T cell clones between tumor and peripheral blood	O (Tissue) M (Blood)	<u>Fresh tumor core biopsy</u> Archival tissue will be used for patients who have insufficient fresh tissue or who refuse the biopsy (8-10 FFPE tissue slides, 10-micron sections) • Day -14 (prior to starting study therapy) • C3D1 (after 12 weeks of CaboNivoIpi therapy) Time points are ±5 days <u>Peripheral Blood</u> • Day -14 (prior to starting study therapy), • C1D1 (after the 2-week XL184 [cabozantinib] run-in and prior to initiation of CaboNivoIpi), • C3D1 (After 12 weeks of CaboNivoIpi therapy) • At progression Time points are ±3 days	Solid Tumor Translational Science Shared Resource PI: Pravin J. Mishra, Ph.D. Pravin.Mishra@osumc.edu

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Point(s)*	Laboratory Performing Assay
4.	PD-1/PD-L1 expression	IHC	Exploratory To correlate treatment response (RECIST v1.1) with pre-treatment PD-1/PD-L1 levels in the primary/metastatic tumor.	O	Fresh tumor core biopsy (4 FFPE tissue slides, 4-micron sections) Archival tissue will be used for patients who have insufficient fresh tissue or who refuse the biopsy • Day -14 (prior to starting study therapy) • C3D1 (after 12 weeks of CaboNivoIpi therapy) Time points are ±5 days	The Ohio State University Histology/IHC Lab Lab PI: Anil Parwani, M.D. Anil.Parwani@osumc.edu
5.	Peripheral Blood Mononuclear Cells (PBMCs)	Multiparameter flow cytometry	Exploratory To evaluate the effect of XL184 (cabozantinib) alone and of CaboNivoIpi on PBMCs and to correlate with treatment response (RECIST v1.1).	M	Peripheral Blood • Day -14 (prior to starting study therapy), • C1D1 (after the 2-week XL184 [cabozantinib] run-in and prior to initiation of CaboNivoIpi), • C3D1 (After 12 weeks of CaboNivoIpi therapy) • At progression Time points are ±3 days	The Ohio State University Flow Cytometry Lab PI: Gerard Lozanski, M.D. Gerard.Lozanski@osumc.edu
6.	Circulating Myeloid Derived Suppressor Cells (MDSCs)	Multiparameter flow cytometry	Exploratory To evaluate the effect of XL184 (cabozantinib) alone and of CaboNivoIpi on MDSCs and to correlate with treatment response (RECIST v1.1).	M	Peripheral Blood • Day -14 (prior to starting study therapy), • C1D1 (after the 2-week XL184 [cabozantinib] run-in and prior to initiation of CaboNivoIpi), • C3D1 (After 12 weeks of CaboNivoIpi therapy) • At progression Time points are ±3 days	The Ohio State University Flow Cytometry Lab PI: Gerard Lozanski, M.D. Gerard.Lozanski@osumc.edu
7.	Tumor Genotyping	Next generation sequencing	Exploratory To correlate treatment response (RECIST v1.1) with tumor mutation status	O	Fresh tumor core biopsy Archival tissue will be used for patients who have insufficient fresh tissue or who refuse the biopsy (7-10 FFPE tissue slides, 10-micron sections) • Day -14 (prior to starting study therapy)	Solid Tumor Translational Science Shared Resource PI: Pravin J. Mishra, Ph.D. Pravin.Mishra@osumc.edu

* All correlative studies will only be done in Stage 2 (14 patients only), after the interim efficacy endpoint is met.

5.8 Integrated Correlative Study

5.8.1 RNA Sequencing (RNAseq)

5.8.1.1 Specimen Receipt and Processing at the ETCTN Biorepository

Tumor tissue received in formalin will be paraffin-embedded at Baseline and C3D1 time points. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide, and for nucleic acid extractions, additional RNase-free slides.

DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to determine concentration and quality. An aliquot of RNA will be shipped to the National Clinical Laboratory Network (NCLN) Genomics Laboratory for analysis. Samples may be shipped quarterly.

5.8.1.2 Site Performing Correlative Study

RNA sequencing will be performed at the NCLN Genomics Laboratory.

5.8 Exploratory/Ancillary Correlative Studies

5.8.1 Tumor Infiltrating Lymphocytes (TILs)

We propose to study the correlation between frequency of TILs in biopsies taken pre-treatment and after 12 weeks of CaboNivoIpi therapy and treatment response. This will be studied using IHC on fresh tumor biopsies, preferably obtained from a metastatic site. We hypothesize that XL184 (cabozantinib) will initially induce immunogenic cell death which will bolster anti-tumor T cell responses and the subsequent addition of nivolumab and ipilimumab after 2 weeks will further augment this response. Given the exploratory nature of this correlative analysis, the option to consent for a fresh tumor biopsy for this testing will only available in Stage 2 (that is, only if we see preliminary evidence of efficacy of CaboNivoIpi in Stage 1). While the sample size is small, these exploratory findings may help yield valuable results.

5.8.1.1 Specimen Receipt and Processing at the ETCTN Biorepository

Tumor tissue received in formalin will be paraffin embedded. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. Eight to 10 charged slides, cut at 4 microns, will be required for TILs analysis. TIL analysis will be considered a first testing priority for patients who refuse to have a biopsy performed.

FFPE tissue slides for TILs analysis should be shipped quarterly to:

Attn: Christina Hopkins
410 W. 10th Ave. Doan Hall
Rm N322
Columbus, OH 43210
Tel: 614-293-1764
Email: Christina.Hopkins@osumc.edu

5.8.1.2 Site Performing Correlative Study

TIL marker staining assays will be performed in the Ohio State University Histology Lab under the direction of Dr. Anil Parwani.

The presence of TILs will be assessed using antibodies for CD4 and CD8 proteins. The clinically established CD4 antibody is mouse monoclonal clone 1F6 recombinant protein immunogen directed to the IgG1 isotype purchased through Abcam. The clinically established CD8 antibody is mouse monoclonal clone C8-144B synthetic peptide protein directed to the IgG1 purchased through Dako (Agilent). The CD4 and CD8 biomarkers are performed according to clinically established and validated protocols using a Leica Bond III system on 4-micron sections of tissue placed onto charged slides. Additionally, we will perform related TIL marker staining on CD3 and FoxP3 using established antibodies and protocols.

5.8.2 PD-1/PD-L1 testing

We propose to correlate CaboNivoIpi treatment response (as assessed by RECIST v1.1) with pre-treatment PD-1/PD-L1 levels in the primary/metastatic tumor in patients with advanced DTC. PD-L1 overexpression has been shown to predict treatment response to immune checkpoint inhibitors in multiple tumor types (Meng *et al.*, 2015). We plan to perform IHC for expression of PD-1 and PD-L1 in tissue. Given that PD-1/PD-L1 expression is a dynamic process, and is affected by immune checkpoint inhibitor therapy (Vilain *et al.*, 2017), we will evaluate PD-1 and PD-L1 using IHC on fresh tumor tissue, preferably from a metastatic site, obtained at baseline (prior to Day -14) and at Cycle 3 Day 1. In patients who refuse a baseline biopsy, archival tissue will be used for evaluation of PD-1/PD-L1 status at baseline.

5.8.2.1 Specimen Receipt and Processing at the ETCTN Biorepository

Tumor tissue received in formalin will be paraffin-embedded at Baseline and C3D1 time points. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. Four charged slides, cut at 4 microns, will be required for PD-1/PD-L1 analysis. If a biopsy at Baseline is not submitted, then unstained slides from Archival tissue will be used for this assay. Slides should be baked for 1 hour in a 60◦C oven. Slides should be stored at 4◦C for long term storage. Slides that have been cut and stored for a long time may lose their antigenicity and stain weaker, or may not stain at all.

FFPE tissue slides should be shipped quarterly with gel packs to:

Attn: Christina Hopkins
410 W. 10th Ave.
Doan Hall Rm N322
Columbus, OH 43210
Tel: 614-293-1764
Email: Christina.Hopkins@osumc.edu

5.8.2.2 Site Performing Correlative Study

PD-1/PD-L1 assays will be performed in the Ohio State University Histology Lab under the direction of Dr. Anil Parwani. PD-L1 assays are performed using a Dako Link 48 system with 4-micron tissue sections on charged slides. This marker is deparaffinized online using the Dako PT link low pH retrieval. The slides are then processed using the Dako Link PD-L1 22C3 pharmDx FDA approved kit.

For the PD1 assay, FFPE tissue cut at 4-micron sections on positive charged slides should be submitted to the OSU IHC lab for PD-1 and will be processed using Leica Bond III instruments. Each test is routinely deparaffinized and retrieved online using Leica Bond Dewax and 100% alcohol. PD-1 is then assessed using a routine clinically validated protocol that uses the Leica Bond Polymer Refine Detection system and a 30-minute antibody incubation time. Tissue is then dehydrated, and cover slipped. The OSU IHC lab uses PD-1 (clone NAT105) purchased through Cell Marque. PD-1 is a mouse monoclonal type-1 transmembrane protein directed towards the IgG1 isotype.

5.8.3 T-cell clonality

We propose to evaluate the effect of CaboNivoIpi on TCR repertoire and to identify the frequency of shared T cell clones between tumor and peripheral blood using next generation TCR sequencing and single cell sequencing. We also plan to define the molecular characteristics of individual T cell clones through single cell transcriptomics (Savas *et al.*, 2018). Using serial DNA samples extracted from PBMCs and tumor samples of patients on the drug arm, we will comprehensively characterize their T cell receptor repertoire at baseline and then serially during the trial period. We will compare the diversity and dynamics of the T cell repertoire in responders *versus* non-responder and also assess their correlation with changes in mutational/neoantigen burden during treatment.

5.8.3.1 CPT Blood Specimen Receipt and Processing at the ETCTN Biorepository

Whole blood received in CPT tubes will be processed with Ficoll to isolate PBMCs. After isolation, PBMCs will be slow frozen and stored in a liquid nitrogen vapor phase freezer.

After processing, samples should be shipped frozen quarterly to:

Solid Tumor Translational Science Shared Resource
460 W, 12th Avenue, BRT 240
Columbus, OH, 43210.

5.8.3.2 Core Biopsy Sample Receipt and Processing at the ETCTN Biorepository

Formalin-fixed tissue at Baseline will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the ETCTN Biorepository, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if

needed, and scraped for DNA extraction. DNA will be banked in a stock vial and stored in a -80°C freezer until distribution for testing.

If only Archival tissue is submitted, then the Biorepository will perform pathology review, macrodissection, and co-extraction as described above.

DNA from tumor tissue should be shipped quarterly to:

Solid Tumor Translational Science Shared Resource
460 W, 12th Avenue, BRT-240
Columbus, OH, 43210.

5.8.3.3 Site Performing Correlative Study

Using serial DNA samples extracted from PBMC and tumor samples of patients on study treatment, we will comprehensively characterize their T cell receptor repertoire at baseline and then serially during the trial period. We will compare the diversity and dynamics of the T cell repertoire in responders *versus* non-responder and also assess their correlation with changes in mutational/neoantigen burden during treatment.

In order to examine all possible variable, diversity, and joining (V[D]J) segments of the T cell receptor combinations, we will use a switching mechanism at 5' end of RNA transcript and rapid amplification of cDNA ends (SMART RACE) library construction kit (Clontech). PCR amplification of *TCRA* and *TCRB* gene products with adapter-conjugated primer sets will be used to prepare amplicon libraries a compatible with the Illumina NGS platform. The template library will then be amplified by Nextera XT index kit (Illumina) that allows barcode tagging and pooling of up to 16 samples. The prepared library will be analyzed using an Illumina MiSeq system. The output data will be analyzed using Tcrip software or MiTCR.

Using DNA extracted from frozen tumor/PBMC samples, we will perform next-generation sequencing of TCR β chain. Briefly, we will synthesize cDNA with 5' rapid amplification of end (5'-RACE) adapter using SMART cDNA library kit (Clontech) and Advantage 2 Polymerase (Clontech) following manufacturer's protocol. We will then amplify the TCR- β gene products with a reverse primer specific for the constant region and a forward primer for the SMART adapter. In order to be able to pool samples, we will apply sequence adapters with barcode sequence using Nextera XT Index kit (Illumina). We will then perform sequencing by 300-pb paired-end reads on the MiSeq platform (Illumina). We will use Tcrip software for the TCR β repertoire analysis. First, we will separately map the read to the International ImMunoGeneTics reference sequences of the variable (V), joining (J) and constant (C) using Bowtie 2 aligner. After determining the junction sequence between the V and J segments, the D segment in this sequence will be identified by scoring similarities of sub-sequences with reference sequences using sliding window method following which N1 and N2 segments will be determined. The amino acid sequences of the CDR3 regions will be determined starting with the second conserved cysteine in the V segment and ending with the conserved phenylalanine in the J segment. We will use Excel (Microsoft) to calculate clonal frequencies and draw pie/line chart.

This assay will be performed in the Solid Tumor Translational Science Shared Resource at the Ohio State University Comprehensive Cancer Center.

5.8.4 Peripheral Blood Mononuclear Cells and Myeloid-Derived Suppressor Cells

We propose to evaluate the effect of XL184 (cabozantinib) and of CaboNivoIpi on PBMCs and MDSCs and to correlate these effects with treatment response. Immune checkpoint inhibitors have been shown to have an anti-tumor effect through inducing the proliferation of pre-existing T cells (Tumeh *et al.*, 2014; Zitvogel *et al.*, 2013). There is emerging evidence that the clinical benefits of conventional chemotherapies and kinase inhibitors may be partly mediated by their impact on the immune system (Forde *et al.*, 2018). In a phase 2 study of XL184 (cabozantinib) in advanced/metastatic urothelial cancer (NCT01688999), patients with low levels of T_{regs} at baseline had better treatment response, PFS, and OS compared to those with high baseline levels (Apolo *et al.*, 2014).

Cellular Immunome® characterization by multi-color flow cytometric analysis is a method developed at the Ohio State University Medical Center (OSUMC) Clinical Flow Cytometry Laboratory that uses ~60 markers (10 colors), in order to detect more than 800 different populations of immune cells in peripheral blood. These immune subsets include cells such as natural killer (NK) cells, CD4+ T cells, CD8+ T cells, T_{regs}, MDSCs, dendritic cells, and other myeloid cells at various stages of maturation/senescence (including naive stage, early/mid/late activation, memory stage, senescent stage, *etc.*). Cellular Immunome analyses using 5- and 10-color methods have been developed and validated according to strict CAP requirements in CAP/CLIA-approved clinical flow cytometry laboratory.

5.8.4.1 Specimen Receipt and Processing at OSU Flow Cytometry Lab

This method involves flow cytometric analysis of the collection of 10 ml of peripheral whole blood. The blood will be collected in one (1), 10 ml purple top EDTA, vacutainer tube: The sample will be shipped unprocessed within 48 hours of collection to:

OSU Flow cytometry Lab 410 W 10th Ave, 303 Doan
Attn: Rhonda Kitzler/Becky Pearson
Columbus, OH 43210

Rhonda L Kitzler
Tel: 614-366-1597
Email: rhonda.kitzler@osumc.edu

Becky Pearson
Tel: 614-366-7677
Email: rebecca.pearson@osumc.edu

5.8.4.2 Site Performing Correlative Study

Assays will be performed at The Ohio State University Flow Cytometry Lab using the Immunome assay, including MDSC analysis, under the direction of Dr. Gerard Lozanski, who is a board-certified hematopathologist with expertise in flow cytometry analysis.

5.8.5 Tumor Genotyping

Close to 70% of DTC have somatic genomic alterations in *RET*, *NTRK1*, *BRAF*, or *RAS* (Kondo *et al.*, 2006). Whether somatic genomic alterations predict response to XL184 (cabozantinib) in combination with nivolumab and ipilimumab in RAI refractory DTC is unknown. We propose to correlate treatment response with tumor mutational status in archival tissue from patients with advanced DTC.

5.8.5.1 Specimen Receipt and Processing at the ETCTN Biorepository

Formalin-fixed tissue at Baseline will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the ETCTN Biorepository, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

If only Archival tissue is submitted, then the Biorepository will perform pathology review, macrodissection, and co-extraction as described above.

DNA from tumor tissue should be shipped quarterly to:

Solid Tumor Translational Science Shared Resource
PI: Pravin J. Mishra, Ph.D.
460 W. 12th Avenue
BRT-240
Columbus, OH 43210
Tel: 614-366-9041 / 732-425-2820
Email: Pravin.Mishra@osumc.edu

5.8.5.2 Site Performing Correlative Study

Assay will be performed in the laboratory of Dr. Pravin Mishra at the Solid Tumor Translational Science Shared Resource. This shared resource has designed and developed a targeted cancer panel that encompasses 400 genes using Agilent probes and indexes.

The library will be prepared according to standardized protocols using the Kapa Hyper library preparation kit. After the library is prepared it will be processed and sequenced on the HiSeq platform (Ilumina). The results will be analyzed using pre-established and validated bioinformatics pipelines.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Treatment must begin within 2 weeks of registration Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	Premedications and Precautions	Dose	Route	Schedule	Cycle Length
XL184 (cabozantinib)	XL184 (cabozantinib) should be taken on an empty stomach. Patients should not eat for at least 2 hours before, and 1 hour after each dose.	40 mg	PO	Run-in: Days -14 to -1 (pre-Cycle 1 only) Cycles 1-4: Days 1-42 Cycles 5+: Days 1-28	N/A
Nivolumab	N/A	240 mg	IV	Days 1, 15, and 29 of Cycles 1-4 (12 total doses)	42 days (6 weeks)
Ipilimumab	N/A	1 mg/kg	IV	Day 1 of Cycles 1-4 (four total doses)	
Nivolumab	N/A	480 mg	IV	Day 1 of Cycles 5+	28 days (4 weeks)

The purpose of a 2-week XL184 (cabozantinib)-only run-in period is to allow for study of the effect of XL184 (cabozantinib) on the tumor microenvironment and to optimize management of early toxicities of XL184 (cabozantinib) before addition of combination therapy. Hypertension is commonly seen with XL184 (cabozantinib), and is seen early on during treatment.

Peripheral blood will be evaluated (PBMCs, MDSCs, T-cell clonality) before and after the 2-week XL184 (cabozantinib)-only run-in period, which could provide valuable information on the immunomodulatory role of XL184 (cabozantinib).

6.1.1 XL184 (cabozantinib)

Patients will receive XL184 (cabozantinib) PO at a dose of 40 mg once daily. XL184 (cabozantinib) must be taken on an empty stomach. Patients should be instructed not to eat for at least 2 hours before and at least 1 hour after taking XL184 (cabozantinib). Patients should be instructed to take their dose at approximately the same time every day. If a patient misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next

scheduled dose. If a patient vomits after taking a dose, the dose should not be made up. The patient should be instructed to take the next dose at the regularly scheduled time.

XL184 (cabozantinib) tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by patients taking XL184 (cabozantinib). Patients will be asked to maintain a medication diary for each dose of medication (Appendix D). The medication diary should be returned to clinic staff at the end of each month.

Dose reductions and delays to manage toxicity are allowed under the guidelines in Section 7.1 below. XL184 (cabozantinib) administration will continue until disease progression or unacceptable toxicity.

6.1.2 Nivolumab

Nivolumab will be given every 2 weeks (±3 days) at a dose of 240 mg on Days 1, 15, and 29 of each 6-week cycle for the first 4 cycles (24 weeks). Starting with Cycle 5, nivolumab will be given every 4 weeks (±3 days) at a dose of 480 mg on Day 1 of each 4-week cycle. Patients may not be dosed fewer than 12 days from the previous dose of drug. Nivolumab administration will continue until disease progression or unacceptable toxicity.

Nivolumab is to be administered as an approximately 30-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter. The drug can be diluted with 0.9% normal saline or 5% dextrose in water for delivery. Fixed doses (e.g., 240 mg, or 480 mg) of nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 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.

When infusions of ipilimumab and nivolumab are given on the same day, the preferred treatment is to give nivolumab followed by ipilimumab. Separate infusion bags and filters must be used for each drug. The infusion line must be flushed with normal saline between infusions.

Toxicity management should follow the guidelines and algorithms that are provided in Section 7 and Appendix C.

6.1.3 Ipilimumab

Ipilimumab is to be administered as an approximately 90-minute IV infusion at a dose of 1 mg/kg on Day 1 (±3 days) of each 6-week cycle for the first 4 cycles (24 weeks), using a volumetric pump with a 0.2-1.2 micron in-line filter. Ipilimumab should always be administered immediately following nivolumab administration. The drug can be diluted with 0.9% normal saline for delivery or 5% dextrose in water, but the total drug concentration of the solution must stay within the range of 1 mg/mL to 4 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. No more than four doses of ipilimumab should be administered.

Dosing calculations should be based on the actual body weight. If the patient's weight differs by >10% from the weight used to calculate the original dose, the dose may be recalculated. All doses should be rounded to the nearest 5 milligram.

Toxicity management for ipilimumab should follow the same guidelines and algorithms that are provided in Section 7 and Appendix C.

6.1.4 Other Agent(s)

TSH suppression will continue throughout study and should be administered according to local institutional standards.

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of XL184 (cabozantinib) with other concomitantly administered drugs, the CRF must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. For example, the potential targets for drug interaction can involve, but are not limited to CYPs 450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors. Check the Investigator's Brochures for each study agent for potential sources of drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Clinical Trial Wallet Card) should be provided to patients if available.

6.2.1 Concomitant Medications and Therapies

6.2.1.1 Anticancer Therapy

If a patient requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Patients receiving local intervention (*e.g.*, palliative radiation) to non-target lesions are allowed to continue to receive study treatment at the treating physician's discretion. Patients may discontinue study treatment while receiving palliative radiation therapy to a bone lesion, then restart study treatment if the treating physician and overall study PI agree that there is potential for further clinical benefit. Only patients who have unequivocal progression in bone will be classified as having PD.

6.2.1.2 Other Medications

Patients must be instructed to inform the treating physicians 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 treating physician to ensure that details regarding all medications are documented.

Bisphosphonates or denosumab started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution. Start date and end dates for such treatments must be documented.

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors [G-CSF]) and pain medications administered as dictated by standard practice are acceptable while the patient 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.

6.2.1.3 Potential Drug Interactions

6.2.1.3.1 Cytochromes P450

Co-administration of XL184 (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 XL184 (cabozantinib) concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 (*e.g.*, chronic use of modafinil) should be used with caution because these drugs have the potential to decrease exposure to XL184 (cabozantinib). 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 patient who has been concurrently receiving a stable dose of XL184 (cabozantinib), as this could significantly increase the exposure to XL184 (cabozantinib).

Strong CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure to XL184 (cabozantinib). Grapefruit, grapefruit juice, and Seville oranges may also increase plasma concentrations of XL184 (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 CYPs (*e.g.*, CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter XL184 (cabozantinib) exposure is not known. Therefore, these drugs should be used with caution when given with XL184 (cabozantinib).

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. 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.

6.2.1.3.2 Protein Binding

XL184 (cabozantinib) is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly-protein-bound drugs should be used with caution with XL184 (cabozantinib) because the potential displacement interaction could increase free concentrations of XL184 (cabozantinib) and/or co-administered highly protein-bound drugs and lead to corresponding

increases in pharmacologic effect(s). Factors that influence plasma protein binding may affect individual tolerance to XL184 (cabozantinib). 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 narrow therapeutic index, administration of warfarin at therapeutic doses should be avoided in patients receiving XL184 (cabozantinib) due to the potential for a protein binding displacement interaction.

6.2.1.3.3 Drugs Associated with QTc Prolongation

Treatment with XL184 (cabozantinib) has been associated with a mild prolongation of the QTc interval. Caution should be used when treating patients on XL184 (cabozantinib) with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for patients who are treated concomitantly with QTc-prolonging drugs.

6.2.1.3.4 Other Interactions

Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids has had no clinically relevant effect on XL184 (cabozantinib) plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 (cabozantinib) is allowed.

In vitro data suggest that XL184 (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 most recent version of the XL184 (cabozantinib) Investigator's Brochure.

6.3 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue until one of the following criteria applies:

- Disease progression
  - To account for potential pseudo-progression with immunotherapy, patients who are deriving clinical benefit from the study treatment may be permitted to continue treatment beyond initial RECIST 1.1-defined PD as defined in Section 6.6 as defined in Section 6.6.
- Intercurrent illness that prevents further administration of treatment
- AE(s) which require(s) permanently going off study treatment (see also Section 7 and specific algorithms in Appendix C)
- Dosing interruption unrelated to study treatment lasting >6 weeks. For treatment-related dosing interruptions, please refer to section 6.5. Tumor assessments should continue as per protocol even if dosing is interrupted.
- 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
- Clinical progression

- Patient non-compliance
- 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.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.4 Duration of Follow Up

Patients will be followed for 2 years after discontinuation of study treatment or until death, whichever occurs first. Patients who are taken off study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. The first follow-up will occur 6 weeks after the last dose of study medication, after which patients will be contacted every 12 weeks for follow-up. Follow-up after the first 6-week follow-up visit may be by phone interview.

6.5 Criteria to Resume Treatment

Some patients may continue to benefit from treatment, maintaining or improving responses after progression including those treated with steroids.

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 or 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 8 -week delay period (for ipilimumab/nivolumab treatment- related dose delays) and within the 6-week (for treatment unrelated dose delays or XL184 (cabozantinib) therapy-related dose delays) delay period. Of note: patients who are required to hold XL184 (cabozantinib) due to treatment-related side effects can continue ipilimumab/nivolumab per physician discretion. Also, patients who require to hold ipilimumab/nivolumab due to treatment-related AEs, may continue with XL184 (cabozantinib) treatment per physician discretion.

NOTE:
For patients on CaboNivoIpi with grade 2-3 or selected grade 4 (as detailed in Section 7 below) AEs deemed to be related to nivolumab and/or ipilimumab requiring discontinuation of nivolumab and/or ipilimumab therapy, treatment with nivolumab may resume when the event resolves to baseline at the discretion of the treating investigator. XL184 (cabozantinib) may be continued throughout at the investigator's discretion. Patients on XL184 (cabozantinib) plus nivolumab who develop grade 2-3 or selected grade 4 (as detailed below) AEs deemed to be related to nivolumab and requiring discontinuation of nivolumab therapy may continue treatment with XL184 (cabozantinib) at the investigator's discretion.

For patients treated with high dose steroids:

- The associated AE must resolve to baseline within 6 weeks of treatment.
- The patient must be off steroids or must have tapered down to a dose equivalent of <10mg/day of prednisone.
- There must be no recurrence of symptoms or new symptoms during the steroid taper.

6.6 Treatment Beyond Progression

A minority of patients treated with immunotherapy may derive clinical benefit either delayed responses, stable disease, or increased overall survival despite initial evidence of PD.

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD occurring in the first 12 weeks post-registration, weeks as long as they meet the following criteria:

- No more than 4 new lesions. The total sum of the longest diameter (or short diameter for lymph nodes) cannot exceed 40% of the initial sum including new lesions.
- Patients must be clinically stable with no change in performance status due to disease progression
- No indication for immediate alternative treatment
- The patient (as assessed by the Investigator) is showing clinical benefit and tolerates the study therapy. The assessment of clinical benefit should consider whether the patient is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.
- Patient does not continue to progress at 4-week follow-up imaging after PD (by RECIST v1.1) is first noted.

If progression is confirmed, then the date of disease progression will be the first date the patient met the criteria for progression based on the standard RECIST 1.1 criteria.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter

increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses, this will need to be described in patient response information, *e.g.*, patients who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event but may be designated as delayed responses for purposes of determining ORR and counted as responses for the two-stage design.

7. DOSING DELAYS/DOSE MODIFICATIONS

XL184 (cabozantinib), and nivolumab and ipilimumab have class-specific safety profiles based on their mechanisms of action, but may also cause AEs that overlap. For management of AEs which can be clearly attributed to either XL184 (cabozantinib) or immunotherapy, independent dose modification for either component of study treatment is allowed. Examples of VEGFR TKI-associated AEs caused by XL184 (cabozantinib) are hypertension and hand-foot syndrome. Examples of immune-related AEs caused by nivolumab and ipilimumab are pneumonitis and endocrinopathies. For AEs without clear attribution to either component of study treatment, management of toxicity should include dose modifications of XL184 (cabozantinib) and immunotherapy, at the discretion of the investigator. Examples of overlapping AEs are diarrhea and transaminase increases.

7.1 XL184 (Cabozantinib)

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for XL184 (cabozantinib) is 40 mg/day. Two dose reduction levels of XL184 (cabozantinib) are permitted (see Section 7.1.2).
- Study treatment dose adjustment is only needed if the AE is deemed possibly, probably, or definitely related to XL184 (cabozantinib) treatment.
- Dose modification criteria for XL184 (cabozantinib) are shown below in Section 7.1.2. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a patient is on treatment.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined below, if the investigator feels it is in the interest of a patient's safety and will optimize drug tolerability.
- For patients who require any biopsy procedure, XL184 (cabozantinib) should be held for 2 days (48 hours) prior to biopsy, and may be resumed 2 days (48 hours) following the procedure, unless there is evidence of biopsy wound-related complications or incomplete wound healing. Due to the risk of perforation and fistula with XL184 (cabozantinib),

transesophageal and other transluminal biopsies should not be performed, and biopsies should not be performed in areas of prior fistula formation, surgery, or radiation.

- In patients requiring interruption of XL184 (cabozantinib) treatment due to any reason for >6 consecutive weeks, XL184 (cabozantinib) should be discontinued. In this situation, a patient may continue to receive ipilimumab and/or nivolumab per the discretion of the investigator.
- Patients on CaboNivoIpi who require permanent discontinuation of XL184 (cabozantinib) due to any reason may continue with nivolumab and ipilimumab at the investigator's discretion. Patients on XL184 (cabozantinib) plus nivolumab who require permanent discontinuation of XL184 (cabozantinib) due to any reason may continue with nivolumab at the investigator's discretion.

General guidelines for the management of non-hematologic and hematologic toxicities are provided below.

7.1.1 Potential Adverse Events

Calcium, magnesium, potassium, and phosphorus should be kept above the LLN. For more specific guidelines on GI AEs (GI perforation, GI fistula, intra-abdominal and pelvic abscess, diarrhea, nausea/vomiting, stomatitis/mucositis), non-GI fistula, hepatobiliary disorders, pancreatic conditions, thromboembolic events, hypertension, skin disorders (*e.g.*, palmar-plantar erythrodysesthesia syndrome [PPES]), wound healing and surgery, proteinuria, nervous system disorders, infections and infestations, corrected QT prolongation, electrolyte disorders, and endocrine disorders, refer to Section 7.1.3 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.

Patients will be monitored for AEs from the time of signing informed consent through their last follow-up visit. Patients will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v5.0. Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption.

The most frequent AEs experienced by ≥20% of patients treated with XL184 (cabozantinib) in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of XL184 (cabozantinib), refer to the most recent Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (*e.g.,* TIA, and MI) and venous thrombotic AEs (*e.g.,* DVT and PE), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-

abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥5% of patients treated with XL184 (cabozantinib) in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with XL184 (cabozantinib), as the drug is expected to reach steady-state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. AEs should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

XL184 (cabozantinib) should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

7.1.2 General Dose Modifications for XL184 (Cabozantinib)

Dose Reductions of XL184 (cabozantinib)

Dose Level	XL184 (cabozantinib) dose
1	40 mg PO daily
-1	20 mg PO daily
-2	20 mg PO every other day

PO=orally

If a patient experiences several AEs, and there are conflicting recommendations, the treating physician should use the recommended dose adjustment that reduces the dose to the lowest level.

7.1.2.1 XL184 (Cabozantinib) Dose Re-institution and Re-escalation

If the patient recovers from an AE to ≤ grade 1 or to baseline, and the toxicity was deemed at least possibly related to study treatment, then study treatment may be resumed at a reduced dose (see above for the schedule of dose reductions).

Patients receiving a daily dose of 20 mg (Dose Level -1) may resume at the same dose if deemed safe at the investigator's discretion. Patients unable to tolerate Dose Level -1 should be reduced to receiving 20 mg every other day (Dose Level -2).

Re-escalation to the previous XL184 (cabozantinib) dose may be allowed after the first six months of study treatment, at the investigator's discretion, for AEs which have resolved to grade

1 (or baseline) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed after drug-related dose reductions triggered by grade 4 hematological AEs or by grade 4 AEs affecting major organs (*e.g.*, central nervous, cardiac, hepatic, or renal systems). The XL184 (cabozantinib) dose should not exceed 40 mg/day.

7.1.2.2 Dose Modifications for Treatment-Related Non-Hematologic and Hematologic Adverse Events not specified in tables below:

CTCAE v5.0 Grade	Recommended Dose Management
Grade 1 AEs	Add supportive care as indicated. Continue XL184 (cabozantinib) therapy at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are subjectively tolerable and easily managed	Add supportive care as indicated. Continue XL184 (cabozantinib) therapy at the current dose level with supportive care.
Grade 2 AEs which are intolerable to the patient, deemed unacceptable in the treating physician's judgment, or are not easily managed or corrected.	Add supportive care as indicated and reduce the XL184 (cabozantinib) dose by one level. If the AE does not improve to ≤ grade 1 or baseline within 10 days, or worsens at any time, hold XL184 (cabozantinib). Upon resolution to baseline or ≤ grade 1, the previously reduced dose should be restarted. If the AE resolves to ≤ grade 1 or baseline without a dose interruption, continue at the reduced dose.
Grade 3 AEs that occur without optimal prophylaxis or which is easily managed by medical intervention or resolves quickly	-Add supportive care as indicated and hold XL184 (cabozantinib). - For AEs that are easily managed (*e.g.*, electrolyte correction) and resolve to baseline or ≤ grade 1 within 24 hours, XL184 (cabozantinib) may be resumed at either the same dose or one dose level lower, at the investigator's discretion. - If supportive care is required, XL184 (cabozantinib) should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced by one dose level.
Grade 3 AEs that occur despite optimal prophylaxis or are not easily managed by medical intervention	Hold XL184 (cabozantinib) until recovery to ≤ grade 1 or baseline, then resume at one dose level lower.

CTCAE v5.0 Grade	Recommended Dose Management
Grade 4 AEs	For AEs that are easily managed (*e.g.*, correction of electrolytes) with resolution to baseline or ≤ grade 1 within 24 hours, hold XL184 (cabozantinib) until resolution then resume one dose level lower. For other AEs, permanently discontinue XL184 (cabozantinib) unless it is determined that the patient is unequivocally deriving clinical benefit. In this case, upon recovery to ≤ grade 1 or baseline, the patient may be re-treated at a reduced dose, as determined by the treating physician and protocol chair (or co-chair) after consultation with the study sponsor (CTEP).
Note: Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the treating physician believes that it is in the interest of the patient's safety. Note: The dose modification and management guidelines for specific medical conditions are provided below. For re-treatment and re-escalation criteria, see Section 7.1.4.	

7.1.2.3 Dose Modifications for XL184 (Cabozantinib) for Specific Treatment-Related Hematologic Adverse Events

Neutropenia	Recommended Guidelines for Management
Grade 3 with documented infection, Grade 3 lasting ≥5 days or Grade 4	Hold XL184 (cabozantinib) until resolution to ≤ grade 1, then resume with a one dose level reduction.

Thrombocytopenia	Recommended Guidelines for Management
Grade 3 with clinically significant bleeding or Grade 4	Hold XL184 (cabozantinib) until platelet count is ≥100,000/mm^3, then resume with a one dose level reduction.

Febrile Neutropenia	Recommended Guidelines for Management
Grade 3	Hold XL184 (cabozantinib) until recovery of ANC to ≤ grade 1 and temperature to ≤38 °C and resume with a one dose level reduction. Provide supportive care as indicated.
Grade 4	Permanently discontinue XL184 (cabozantinib) therapy unless the investigator determines that the patient is unequivocally deriving clinical benefit. In this case, upon recovery to ≤ grade 1, the patient may be re-treated at a reduced dose, as determined by the treating physician and protocol chair (or co-chair) in consultation with the study sponsor (CTEP).

Anemia	Recommended Guidelines for Management
Grade 4	Permanent XL184 (cabozantinib) discontinuation for grade 4 anemia is not required. Dose reductions or delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.

Other Hematological AEs	Recommended Guidelines for Management
Grade 4	Permanently discontinue XL184 (cabozantinib) therapy unless the investigator determines that the patient is clearly deriving clinical benefit. In this case, upon recovery to ≤ grade 1 or baseline, the patient may be re-treated at a reduced dose, as determined by the treating physician and protocol chair (or co-chair) in consultation with the study sponsor (CTEP).

7.1.3 Guidelines for Management of Potential Adverse Events

7.1.3.1 Gastrointestinal Disorders

7.1.3.1.1 Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess

GI perforation/fistula have been reported with FDA-approved drugs that inhibit VEGF pathways as well as with XL184 (cabozantinib). Carefully monitor for episodes of abdominal pain, especially in patients 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:

- 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 (cabozantinib).

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

Permanently discontinue XL184 (cabozantinib) therapy and initiate appropriate management in patients who have been diagnosed with GI perforation or fistula.

Rectal and perirectal abscesses have been reported, sometimes in patients with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. XL184 (cabozantinib) should be held until adequate healing has taken place.

7.1.3.1.2 Diarrhea

Patients 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/antimotility agents is recommended at the first sign of treatment-related diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in patients with diarrhea that is refractory to the above include deodorized tincture of opium and colestipol. Some patients may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. Infectious work-up may be carried out as needed per physician discretion. Dose modification guidelines for non-hematologic AEs should be followed. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with XL184 (cabozantinib). Infections of the perianal region should be treated per local guidelines.

7.1.3.1.3 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 for non-hematologic AEs in Section 7.1.1.1 should be followed. 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists and glucocorticoids can interact with CYP3A4 and thus change XL184 [cabozantinib] exposure). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. Please note that caution should be used when using ondansetron (a 5-HT3 antagonist) as it can prolong QTc intervals. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte imbalances should be implemented.

7.1.3.1.4 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before XL184 (cabozantinib) therapy 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 XL184 (cabozantinib) therapy, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (*e.g.,* with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

7.1.3.2 Non-Gastrointestinal Fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in patients undergoing treatment with VEGF pathway inhibitors. In addition, patients who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs. Permanently discontinue XL184 (cabozantinib) therapy and initiate appropriate management in patients who have been diagnosed with a non-GI fistula.

7.1.3.3 Hepatobiliary disorders

7.1.3.3.1 Elevation of aminotransferases (ALT and AST):

Evaluation of patients with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (*e.g.,* liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, or hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

Elevations of transaminases have been observed during treatment with XL184 (cabozantinib). In general, it is recommended that patients with elevation of ALT, AST, and/or bilirubin have more frequent liver function tests (LFTs). If possible, hepatotoxic concomitant medications and alcohol should be discontinued in patients who develop elevated transaminases. Since patients may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase Elevation	Intervention
Grade 1	No change in XL184 (cabozantinib) dose, and no additional tests unless clinically indicated.
Grade 2	Continue XL184 (cabozantinib) with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within grade 2, hold XL184 (cabozantinib), and continue with at least weekly LFTs until improvement to ≤ grade 1. XL184 (cabozantinib) may then be resumed with a one dose level reduction.
Grade 3	Hold XL184 (cabozantinib) and monitor with at least twice weekly LFTs until ≤ grade 2, then with at least weekly LFTs until ≤ grade 1. XL184 (cabozantinib) may then be resumed with a one dose level reduction.

Transaminase Elevation	Intervention
Grade 4	Permanently discontinue XL184 (cabozantinib) therapy. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until improvement to ≤ grade 1. If the patient was unequivocally deriving clinical benefit, XL184 (cabozantinib) may be restarted at a reduced dose, as determined by the treating physician and protocol chair (or co-chair) in consultation with the study sponsor (CTEP).

XL184 (cabozantinib) treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2-3 times per week) and XL184 (cabozantinib) should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR <1.5 × ULN, total bilirubin <1.5 × ULN, aminotransferases ≤ baseline grade).

XL184 (cabozantinib) should be permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation > 1.5 x ULN unless Gilbert's syndrome), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase), or some other explanation of the injury (*e.g.*, viral hepatitis, alcohol hepatitis), as the combined finding represents a signal of a potential for the drug to cause severe liver injury (*i.e.*, Hy's Law cases).

All patients who develop isolated bilirubin elevations of grade 3 should have XL184 (cabozantinib) held until recovery to ≤ grade 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, XL184 (cabozantinib) therapy may continue with a one dose level reduction. In patients without biliary obstruction and grade 4 bilirubin elevation, or with recurrence of grade 3 bilirubin elevation after a dose reduction, XL184 (cabozantinib) therapy must be discontinued.

7.1.3.4 Pancreatic conditions

Amylase and lipase elevations have been observed in clinical studies with XL184 (cabozantinib). The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that patients with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Patients with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations	Intervention
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended.

Asymptomatic Lipase or Amylase Elevations	Intervention
Grade 3	Hold XL184 (cabozantinib) and monitor lipase and amylase twice weekly. Upon improvement to ≤ grade 1 or baseline, XL184 (cabozantinib) therapy may resume at the same dose or one dose level lower, at the investigator's discretion. If re-treatment following grade 3 lipase or amylase elevation is at the same dose and grade 3 or 4 elevations recur, then XL184 (cabozantinib) must be held again until lipase and amylase levels have resolved to ≤ grade 1 or baseline and re-treatment must be with a one dose level reduction.
Grade 4	Hold XL184 (cabozantinib) and monitor lipase and amylase twice weekly. Upon resolution to ≤ grade 1 or baseline, and if resolution occurred within four days, XL184 (cabozantinib) therapy may resume at the same dose or one dose level lower, at the investigator's discretion. If resolution takes more than four days, the dose must be reduced, provided that resolution occurs within 6 weeks. If XL184 (cabozantinib) is resumed at the same dose following a grade 4 lipase or amylase elevation and grade 3 or 4 elevations recur, then XL184 (cabozantinib) must be held again until lipase and amylase have resolved to ≤ grade 1 or baseline and must be resumed with a one dose level reduction.

Pancreatitis	Intervention
Grade 2	Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 3	Hold and monitor lipase and amylase twice weekly. Upon resolution to ≤ grade 1 or baseline, XL184 (cabozantinib) may be resumed with a one dose level reduction, if resolution occurs within 6 weeks.
Grade 4	Permanently discontinue XL184 (cabozantinib) therapy. However, if the patient was unequivocally deriving benefit from XL184 (cabozantinib) therapy, treatment may be restarted at a reduced dose, as determined by treating physician and protocol chair (or co-chair) in consultation with the study sponsor (CTEP).

7.1.3.5 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with XL184 (cabozantinib). Patients should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in XL184 (cabozantinib)-treated patients with brain metastases has not been thoroughly analyzed. Patients

enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms attributable to CNS hemorrhage occur.

XL184 (cabozantinib) therapy should be permanently discontinued in patients with serious and life-threatening bleeding events or recent clinically significant hemoptysis. Treatment with XL184 (cabozantinib) should be held if less severe forms of clinically significant hemorrhage occur. After the cause of hemorrhage has been identified and the risk of bleeding has subsided, XL184 (cabozantinib) may be resumed at a dose agreed to by the protocol chair (or co-chair) and the treating physician. Therapy of bleeding events should include supportive care and standard medical interventions.

7.1.3.6 Thromboembolic events

Thromboembolic events are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and PE have been observed in clinical studies with XL184 (cabozantinib), including fatal events. Patients who develop DVT and/or PE should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with XL184 (cabozantinib) may be resumed at one dose level lower in patients with uncomplicated PE or DVT if it is determined that the patient is deriving clinical benefit from XL184 (cabozantinib) treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Patients with life-threatening DVT or PE should have XL184 (cabozantinib) therapy discontinued unless toxicity can be managed, and the patient is deriving clear clinical benefit as determined by the treating physician in consultation with the study sponsor (CTEP). Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a patient is fully anticoagulated, treatment can be restarted at the investigator's discretion with a one dose level reduction. XL184 (cabozantinib) therapy should be permanently discontinued after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all patients, prophylactic anticoagulation is allowed for individual patients at the investigator's discretion. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (*e.g.,* warfarin or other coumarin-related agents, direct thrombin, direct factor Xa inhibitors, antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection) are not allowed.

Arterial thrombotic events (*e.g.*, TIA, MI) have been observed in studies with XL184 (cabozantinib). Further treatment with XL184 (cabozantinib) should be permanently discontinued in patients who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

7.1.3.7 Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in XL184 (cabozantinib) clinical studies. Decisions to decrease or hold the dose of XL184 (cabozantinib) 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. Patients 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 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 one week (such a visit can be with a local physician or a study physician). BP should be monitored in a constant position visit to visit, either sitting or supine.

XL184 (cabozantinib) should be held in patients 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 should be permanently discontinued in patients with hypertensive emergency. The table below provides treatment guidelines for hypertension deemed related to XL184 (cabozantinib). BP should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. XL184 (cabozantinib) dose modification decisions 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.

Criteria for Dose Modifications	Treatment/XL184 (cabozantinib) Dose Modification
Patients NOT receiving optimized anti-hypertensive therapy	
Systolic ≥140 and <160 mm Hg OR Diastolic ≥90 and <110 mm Hg	Optimize antihypertensive therapy (*i.e.*, increase dose of existing medications and/or add new antihypertensive medications) and continue XL184 (cabozantinib) with no change. If optimal antihypertensive therapy (usually to include three agents) does not result in BP <140 mm Hg systolic and <90 mm Hg diastolic, or if the patient is symptomatic, the dose of XL184 (cabozantinib) should be reduced by one level.
Systolic ≥160 and <180 mm Hg OR Diastolic ≥110 and <120 mm Hg	Reduce XL184 (cabozantinib) by one dose level. Optimize antihypertensive therapy (*i.e.*, increase the dose of existing medications and/or add new antihypertensive medications). Monitor the patient closely for hypotension. If optimal antihypertensive therapy (usually to include three agents) does not result in BP <140 mm Hg systolic and <90 mm Hg diastolic, the dose of XL184 (cabozantinib) should be reduced further.
Systolic ≥180 mm Hg OR Diastolic ≥120 mm Hg	Hold XL184 (cabozantinib) and add new or additional anti-hypertensive medications and/or increase the dose of existing medications. Monitor the patient closely for hypotension. When BP <140 mm Hg systolic and <90 mm Hg diastolic, resume XL184 (cabozantinib) treatment with a one dose level reduction. If optimal antihypertensive therapy (usually to include three agents) does not result in BP <140 systolic or < 90 diastolic, the dose should be reduced further.

Criteria for Dose Modifications	Treatment/XL184 (cabozantinib) Dose Modification
Hypertensive emergency*	Permanently discontinue XL184 (cabozantinib) therapy.
* Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (*e.g.,* myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, or kidney damage). Note: If systolic and diastolic BP meet different criteria in the table, manage according to the higher dose-modification criterion. Note: In patients deemed to have a component of white coat hypertension, a home BP log can be used at the investigator's discretion.	

7.1.3.8 Palmar-plantar erythrodysesthesia syndrome (PPES)

PPES (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 with XL184 (cabozantinib). All patients on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry. Early manifestations include tingling, numbness, mild hyperkeratosis, and 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. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized below.

PPES	Action to be Taken
Grade 1	XL184 (cabozantinib) may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, the XL184 (cabozantinib) dose should be reduced by one level. Start or continue treatment with urea 20-40% cream twice daily and high potency steroid cream (e.g. clobetasol 0.05% cream twice daily). A topical lidocaine 5% ointment or NSAIDs/GABA agonists/narcotics may also be used for pain control. Patients should be reassessed at least weekly for changes in severity. Patients should be instructed to notify their treating physician immediately if severity worsens.

PPES	Action to be Taken
Grade 2	XL184 (cabozantinib) may be continued at the same dose level if PPES is tolerated. The XL184 (cabozantinib) dose should be reduced or held if PPES is intolerable. Start or continue treatment with urea 20-40% cream twice daily and high potency steroid cream (e.g. clobetasol 0.05% cream twice daily). A topical lidocaine 5% ointment or NSAIDs/GABA agonists/narcotics may also be used for pain control. Patients should be reassessed at least weekly for changes in severity. If XL184 (cabozantinib) was held (but not reduced), it may be resumed at the same dose or one dose level lower upon resolution to ≤ grade 1. If a second interruption is required, the XL184 (cabozantinib) dose must be reduced by one level when treatment resumes. Patients should be instructed to notify their treating physician immediately if the severity worsens. If the severity worsens at any time, or affects self-care, proceed to the management guidelines for grade 3 PPES.
Grade 3	Hold XL184 (cabozantinib) until severity decreases ≤ to grade 1. Start or continue treatment with urea 20-40% cream twice daily and high potency steroid cream (e.g. clobetasol 0.05% cream twice daily). A topical lidocaine 5% ointment or NSAIDs/GABA agonists/narcotics may also be used for pain control. Resume XL184 (cabozantinib) at one dose level lower upon resolution to ≤ grade 1. Permanently discontinue XL184 (cabozantinib) therapy if PPES worsens or does not improve within 6 weeks.

7.1.3.9 Osteonecrosis

Osteonecrosis has been reported in patients treated with XL184 (cabozantinib). Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis. Advise patients regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in patients receiving bisphosphonates.

Invasive dental procedures should be avoided. 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 (cabozantinib). If clinically possible, treatment with XL184 (cabozantinib) should be interrupted for at least 4 weeks prior to the

procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Patients with any documented case of osteonecrosis should stop XL184 (cabozantinib) therapy, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by the study sponsor (CTEP) on a case by case basis

7.1.3.10 Wound healing and surgery

XL184 (cabozantinib) has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical, and traumatic wounds must not only be completely healed prior to starting XL184 (cabozantinib) treatment but must also be monitored for wound dehiscence, wound infection, and other signs of impaired wound healing while the patient is being treated. If dehiscence occurs, XL184 (cabozantinib) treatment should not be restarted until complete healing has taken place.

Treatment with XL184 (cabozantinib) must be interrupted for any wound healing complication which needs medical intervention. Treatment with XL184 (cabozantinib) can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. XL184 (cabozantinib) should be discontinued in patients 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 (cabozantinib) should be stopped at least 3 weeks (5 half-lives) prior to elective major surgery. The decision to resume treatment with XL184 (cabozantinib) after surgery should be based on clinical judgment of adequate wound healing.

7.1.3.11 Proteinuria

Proteinuria has been reported with XL184 (cabozantinib). Proteinuria should be monitored by measuring UPCR. The following table provides treatment guidelines for proteinuria deemed related to XL184 (cabozantinib). XL184 (cabozantinib) should be permanently discontinued in patients who develop nephrotic syndrome (proteinuria >3.5 grams per day in combination with hypoalbuminemia, edema, and hyperlipidemia).

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤1 mg/mg (≤113.1 mg/mmol)	No change in XL184 (cabozantinib) dose or UPCR monitoring
>1 and ≤2 mg/mg (>113.1 and ≤226.2 mg/mmol)	No change in XL184 (cabozantinib) dose. A nephrology consultation is recommended. Monitor UPCR once a week. If UPCR ≤1 mg/mg on two consecutive readings, UPCR monitoring can revert to protocol-specific times. The 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 one month, or is determined to be stable (<20% change) for one month, UPCR monitoring can revert to protocol-specific times and as clinically indicated.
>2 and <3.5 mg/mg (>226.2 and <395.9 mg/mmol)	Hold XL184 (cabozantinib). A nephrology consultation is recommended. 24-hour urine protein assessment must be sent off within 7 days. If urine protein is >2 mg/mg, continue to hold XL184 (cabozantinib), check UPCR again within 7 days, and repeat once a week until UPCR decreases to ≤2 mg/mg. Resume XL184 (cabozantinib) at 1 dose level lower once UPCR is ≤2 mg/mg. Repeat UPCR test within 7 days of resuming XL184 (cabozantinib). Monitoring of UPCR 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, UPCR monitoring can revert to protocol-specific times and as clinically indicated.
≥3.5 mg/mg (≥395.9 mg/mmol)	Hold XL184 (cabozantinib). A nephrology consultation is mandatory. 24-hour urine for protein assessment must be sent off within 7 days. If 24-hour urine protein is ≥3.5 mg/mg, continue to hold XL184 (cabozantinib), check UPCR again within 7 days and repeat once a week. If UPCR decreases to ≤2 mg/mg, restart XL184 (cabozantinib) treatment at one dose level lower than previous dose. Repeat UPCR within 7 days of resuming XL184 (cabozantinib). Monitoring of UPCR 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, UPCR monitoring can revert to protocol-specific times and as clinically indicated.
Nephrotic syndrome	Permanently discontinue XL184 (cabozantinib) therapy

7.1.3.12 Nervous System Disorders

XL184 (cabozantinib) appears to represent minimal risk of adverse neurological effects based on nonclinical toxicology studies. However, dysphonia, dysgeusia, headache, dizziness, confused state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with XL184 (cabozantinib). The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported and should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. XL184 (cabozantinib) therapy should be permanently discontinued in patients with RPLS.

7.1.3.13 Infections and Infestations

Infections are commonly observed in cancer patients. Risk factors include decreased immune status (*e.g.*, after myelosuppressive anticancer therapies or splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, and the presence of IV devices. Infections and abscesses should be treated with appropriate local care and systemic therapy. XL184 (cabozantinib) should be held until adequate healing has taken place.

7.1.3.14 QTc Prolongation

Review of the larger safety database (~5000 patients exposed to XL184 (cabozantinib) in clinical trials and in post-marketing experience) showed no safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase XL184 (cabozantinib) plasma concentrations, should be avoided. If at any time on study there is an increase in QTcF to an absolute value >500 msec, two additional EKGs must be performed with intervals not less than 3 min apart within 30 min after the initial EKG. If the average QTcF from the three EKGs is >500 msec, the following actions must be taken:

- Hold XL184 (cabozantinib)
- Hospitalize symptomatic patients (*e.g.,* with palpitations, dizziness, syncope, orthostatic hypotension, or a significant ventricular arrhythmia on EKG) for a thorough cardiology evaluation and management
  - Consider cardiology consultation for asymptomatic patients for evaluation and management
- Check electrolytes, especially magnesium, potassium, and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat EKG triplicates hourly until the average QTcF is ≤500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Patients with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. XL184 (cabozantinib) treatment may be resumed at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation,
- The QTcF value >500 msec is not confirmed,
- XL184 (cabozantinib) has been held through a minimum of 1 week following the return of the QTcF to ≤500 msec,
- QT prolongation can be unequivocally associated with an event other than XL184 (cabozantinib) administration and is treatable/has been resolved.

Once XL184 (cabozantinib) therapy has resumed, EKGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points. XL184 (cabozantinib) therapy must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTc prolongation after re-initiation of study treatment at a reduced dose

7.1.3.15 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with XL184 (cabozantinib), and serum electrolyte levels should be monitored frequently while receiving XL184 (cabozantinib). Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

7.1.3.16 Endocrine Disorders

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with XL184 (cabozantinib) treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Management of thyroid dysfunction (*e.g.*, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders leading to hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of patients. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiating and during XL184 (cabozantinib) therapy is required. XL184 (cabozantinib) therapy should be discontinued in patients with severe or life-threatening endocrine dysfunction.

7.2 Nivolumab and Ipilimumab

Patients receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met (see tables below).

1. In addition to the AEs identified in the tables below, ipilimumab and nivolumab doses should be delayed for any AE, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants a delay.
   (a) Patients who develop alopecia and/or altered taste may continue treatment without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia (nonhemolytic) as it can be satisfactorily managed by transfusion.
2. Patients requiring a delay of >8 weeks due to ipilimumab- and/or nivolumab-related AEs or who experience immune-related toxicity requiring ≥10 mg/day prednisone must permanently discontinue nivolumab and ipilimumab therapy, but may continue XL184 (cabozantinib) therapy.
   (a) Patients who receive systemic corticosteroids for management of any drug-related immunologic toxicity must be off corticosteroids or must have tapered down to a dose equivalent to <10 mg/day prednisone.
3. Patients requiring a delay of >6 weeks due to non-nivolumab- and/or ipilimumab-related AEs should permanently discontinue nivolumab and ipilimumab therapy, but may continue XL184 (cabozantinib) therapy.
4. Doses missed due to adverse events or toxicity will not be made up.
5. Allowance for dose synchronization:
   (a) Nivolumab is allowed to be delayed until the next planned ipilimumab dose <u>if the next ipilimumab dose is scheduled within the next 12 days.</u>
      (i) Nivolumab and ipilimumab doses can be re-synced, at the investigator's discretion, where possible, within the guidance indicated above.
      (ii) This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
      (iii) Patients who require treatment-related delay of nivolumab should be re-evaluated weekly, or more frequently if clinically indicated, and may resume nivolumab dosing when re-treatment criteria are met. Assessments should continue even if dosing is delayed.
   (b) Allowance for ipilimumab dose delays:
      (i) In general, patients who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab with ipilimumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within a ±5-day window, as long as consecutive nivolumab doses are given at least 12 days apart.
      (ii) If an ipilimumab dose is delayed for >6 weeks from the prior dose, then subsequent doses should be rescheduled to maintain at least a 6-week interval between consecutive ipilimumab doses.

(iii) Dosing delays up to 8 weeks to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Assessments should continue even if dosing is delayed.

(iv) In the event that a patient experiences a grade 2 AE while on combination CaboNivoIpi therapy, the patient may resume treatment/may be continued on nivolumab and XL184 (cabozantinib) therapy, at the discretion of the treating investigator (ipilimumab will not be given without nivolumab).

If a patient experiences several AEs, and there are conflicting recommendations, the investigator should use the recommended treatment modification for the most serious event when that has a higher level of modification, *i.e.* discontinuing *versus* holding drug.

Below are AE management tables for nivolumab and combination nivolumab with ipilimumab for the following treatment-related adverse events. Please use as written and contact the drug monitor for any proposed changes.

Please refer to the most recent Nivolumab and Ipilimumab Investigator's Brochures or Appendix C 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. In several places there are differences from the algorithms regarding protocol directed drug modifications. In these cases, please follow the protocol-specific guidelines in this section. Generally, we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

7.2.1 Guidelines for Management of Potential Adverse Events

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change.*	No change.*
Grade 2-3	Hold* nivolumab until ≤ grade 1, then resume.	Hold* both drugs until ≤ grade 1, then resume.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, or 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. Skin rash typically occurs early and may be followed by additional events, particularly during steroids tapering. Recommended management: AE management guidelines.		

Drug-related uveitis, eye pain, blurred vision	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change.*	No change.*
Grade 2	Hold* until < grade 1 or baseline, then resume at same dose. If a grade 2 event does not respond to topical therapy and does not improve to grade 1 within the re-treatment period OR requires systemic therapy, permanently discontinue nivolumab therapy.	Hold both drugs until ≤grade 1 or baseline, then resume at same doses. If grade 2 event does not respond to topical therapy and does not improve to grade 1 within the re-treatment period OR requires systemic therapy, permanently discontinue nivolumab and ipilimumab therapy.
Grade 3	Permanently discontinue nivolumab therapy.	Permanently discontinue ipilimumab and hold nivolumab until ≤ grade 1 and then resume nivolumab monotherapy. If grade 3 event does not respond to topical therapy and does not improve to grade 1 within the re-treatment period OR requires systemic therapy, permanently discontinue nivolumab as well.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Recommended management: AE management guidelines.		

Liver Function AST, ALT, Bilirubin	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	Hold nivolumab, at investigator's discretion, until values return to ULN or baseline, then resume.	Hold both drugs, at investigator's discretion, until values return to ULN or baseline, then resume.
Grade 2 (3-5 × ULN)	Hold nivolumab until values return to baseline or ≤ grade 1, then resume.	Hold both drugs until values return to baseline or ≤ grade 1, then resume.

Liver Function AST, ALT, Bilirubin	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
Grade 3 (5-20 × ULN)	Hold nivolumab and monitor with at least weekly LFTs until grade ≤2. Then resume nivolumab and continue with at least weekly LFTs until improvement to grade ≤ 1. If no improvement is seen, or the condition worsens by 4 weeks, nivolumab should be held, and steroid treatment initiated. If AST/ALT >8 × ULN or bilirubin >5 × ULN, permanently discontinue nivolumab therapy.	Hold both drugs and monitor with at least weekly LFTs until grade ≤2. Then resume both drugs and continue with at least weekly LFTs until improvement to grade ≤1. If no improvement is seen, or the condition worsens by 4 weeks, both drugs should be held, and steroid treatment initiated. If AST/ALT >8 × ULN or bilirubin >5 × ULN, ipilimumab should be permanently discontinued. Manage subsequent events according to nivolumab guidelines.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue ipilimumab and hold nivolumab. Monitor with at least weekly LFTs until grade ≤2, then resume nivolumab. Continue with at least weekly LFTs until improvement to grade ≤1. Manage subsequent dose delays under Management/Next Dose for Nivolumab alone. If no improvement is seen, or the condition worsens by 4 weeks, hold nivolumab and initiate steroid treatment.
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. Note: Grades for liver function follow multiples of ULN, rather than multiples of baseline. Recommended management: see Hepatic AE management algorithm.		

Diarrhea (immune related enterocolitis)	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change.	No change.
Grade 2	Hold nivolumab until ≤ grade 1. Treat symptomatically, and resume nivolumab if improved to ≤ grade 1, at investigator's discretion. If after 4 weeks no improvement is seen, the condition worsens, or colitis is documented by colonoscopy, permanently discontinue nivolumab therapy and initiate steroid treatment.	Hold both drugs until ≤grade 1. Treat symptomatically, and resume both drugs if improved to ≤ grade 1, at investigator's discretion. If after 4 weeks, no improvement is seen, the condition worsens, or colitis is documented by colonoscopy, permanently discontinue ipilimumab and manage according to nivolumab guidelines.
Grade 3	Hold nivolumab until ≤ grade 1 and obtain colonoscopy. Treat symptomatically, and resume nivolumab if colonoscopy shows no colitis and patient improves to ≤ grade 1, at investigator's discretion. If after 4 weeks no improvement is seen, the condition worsens, or colitis is documented by colonoscopy, permanently discontinue nivolumab therapy and initiate steroid treatment.	Permanently discontinue ipilimumab. Hold nivolumab until ≤ grade 1 and obtain colonoscopy. Treat symptomatically, and resume nivolumab if colonoscopy shows no colitis and patient improves to ≤ grade 1, at investigator's discretion. If after 4 weeks no improvement is seen, the condition worsens, or colitis is documented by colonoscopy, permanently discontinue nivolumab therapy and initiate steroid treatment.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should be taken off study treatment. Evaluate pituitary function prior to starting steroids if possible without compromising acute care. Patients should be evaluated for additional causes including *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD at the discretion of the treating physician. Recommended management: see GI AE management Algorithm.		

Amylase/Lipase Increased and Pancreatitis	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1 (Amylase/Lipase Increased Only)	Continue nivolumab therapy, if asymptomatic, at the investigator's discretion.	Continue both drugs, if asymptomatic, at the investigator's discretion.
Grade 2	Continue nivolumab therapy, if asymptomatic, at the investigator's discretion. If symptomatic, resume nivolumab therapy once resolved.	Continue both drugs, if asymptomatic, at the investigator's discretion. If symptomatic, resume nivolumab and ipilimumab therapy once resolved.
Grade 3 Amylase/Lipase Increased	Continue nivolumab, at the investigator's discretion. Monitor lipase and amylase once or twice weekly. Radiographic evaluation is optional if asymptomatic with no evidence of pancreatitis-associated gallbladder disease, no evidence of worsening, or no new onset of DM.	Continue both drugs, at the investigator's discretion. Monitor lipase and amylase once or twice weekly. Radiographic evaluation is optional if asymptomatic with no evidence of pancreatitis-associated gallbladder disease, no evidence of worsening, or no new onset of DM.
Grade 3 Pancreatitis	Continue nivolumab therapy, if asymptomatic, at investigator's discretion. Patients should have imaging done when clinically indicated (*i.e.*, grade 3 pancreatitis) before resuming treatment. Patients who develop symptomatic pancreatitis or DM should permanently discontinue nivolumab therapy.	Continue both drugs, if asymptomatic, at investigator's discretion. Patients should have imaging done when clinically indicated (*i.e.*, grade 3 pancreatitis) before resuming treatment. Patients who develop symptomatic pancreatitis or DM should permanently discontinue nivolumab and ipilimumab therapy.
Grade 4	Hold nivolumab until grade 2. Resume if asymptomatic. Patients should have imaging done before resuming treatment, and when clinically indicated. Patients who develop symptomatic pancreatitis or DM should permanently discontinue nivolumab therapy.	Hold both drugs until grade 2. Resume if asymptomatic. Patients should have imaging done before resuming treatment, and when clinically indicated. Patients who develop symptomatic pancreatitis or DM should permanently discontinue nivolumab and ipilimumab therapy.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and diabetic ketoacidosis. 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 re-treated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm		

Pneumonitis, Bronchospasm, Pulmonary Toxicity, or Interstitial Lung Disease	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	Hold nivolumab pending evaluation and resolution to baseline, including baseline O_2 saturation. Resume after pulmonary and/or infectious disease consultation excludes lymphocytic pneumonitis.	Hold both drugs pending evaluation and resolution to baseline including baseline O_2 saturation. Resume after pulmonary and/or infectious disease consultation excludes lymphocytic pneumonitis.
Grade 2	Hold nivolumab pending evaluation. Resume after pulmonary and/or infectious disease consultation excludes associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should permanently discontinue nivolumab therapy if steroids are required.	Hold both drugs pending evaluation. Resume after pulmonary and/or infectious disease consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should permanently discontinue nivolumab and ipilimumab therapy if steroids are required.
Grade 3	Hold nivolumab pending evaluation. Resume after pulmonary and/or infectious disease consultation excludes associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should permanently discontinue nivolumab therapy if steroids are required.	Hold both drugs pending evaluation. Resume after pulmonary and/or infectious disease consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should permanently discontinue nivolumab and ipilimumab therapy if steroids are required.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab 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. Seasonal influenza killed vaccine is recommended for all patients. The above does not include infusion reactions. Recommended management: See Pulmonary Adverse Event Management Algorithm.		

Other GI Nausea-Vomiting	Management/Next Dose for Nivolumab Monotherapy	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change.	No change.
Grade 2	Hold nivolumab pending evaluation for gastritis duodenitis and other immune AEs or other causes. Resume after resolution to ≤ grade 1.	Hold both drugs pending evaluation for gastritis duodenitis and other immune AEs or other causes. Resume after resolution to ≤ grade 1.
Grade 3	Hold nivolumab until resolution to ≤ grade 1. If symptoms do not resolve within 7 days with symptomatic treatment, permanently discontinue nivolumab therapy.	Hold both drugs until resolution to ≤ grade 1. If symptoms do not resolve within 7 days with symptomatic treatment, permanently discontinue nivolumab and ipilimumab therapy.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Patients with grade 2 or 3 nausea or vomiting should be evaluated for upper GI inflammation and other immune related events.		

Fatigue	Management/Next Dose for Nivolumab Monotherapy	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 2	No change in dose.	No change in dose.
Grade 3	Hold until ≤ grade 2.	Permanently discontinue ipilimumab. Hold both drugs until ≤ grade 2, then resume both drugs.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue both drugs.
Fatigue is the most common adverse event associated with immune checkpoint therapy. Fatigue ≥ grade 2 should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.		

Neurological events	Management/Next Dose for Nivolumab Monotherapy	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	Hold pending evaluation and observation. Resume when resolved to baseline.	Hold both drugs pending evaluation and observation. Resume when resolved to baseline.
Grade 2	Hold nivolumab pending evaluation and observation. Resume when improved to ≤ grade 1 or baseline. Patients should permanently discontinue nivolumab therapy if treatment with steroids is required.	Hold both drugs pending evaluation and observation. Resume when improved to ≤ grade 1 or baseline. Patients should permanently discontinue nivolumab and ipilimumab therapy if treatment with steroids is required.

Neurological events	Management/Next Dose for Nivolumab Monotherapy	Management/Next Dose for Nivolumab plus Ipilimumab
Grade 3	Permanently discontinue nivolumab therapy.	Permanently discontinue ipilimumab. Hold nivolumab until improved to ≤ grade 1 or baseline, then resume. Manage subsequent events according to nivolumab guidelines.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Recommended management: See Neurologic Adverse Event Management Algorithm		

Cardiac*	Management/Next Dose for Nivolumab or Nivolumab plus Ipilimumab
≤ Grade 1	Hold dose pending evaluation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia, or myositis. Obtain history EKG, CK (for concomitant myositis), and CK-MB. Repeat troponin, CK and EKG after 2-3 days. If troponin and labs normalize, patient may resume therapy. If labs worsen or symptoms develop then treat as below.
≥ Grade 2 with suspected myocarditis	Hold dose pending evaluation.** Admit to hospital and consult with a cardiologist. Rule out MI and other causes of cardiac disease. Continue to monitor and obtain echocardiogram. Also consider cardiac MRI and a cardiac biopsy. Initiate high dose methylprednisolone. If no improvement is seen within 24 hours, add either infliximab, ATG, or tacrolimus. Resume therapy if there is a return to baseline AND myocarditis is excluded or considered unlikely.
≥ Grade 2 with confirmed myocarditis	Permanently discontinue nivolumab and ipilimumab therapy and admit to CCU. Treat as above. Consider high dose methylprednisolone and electrophysiology consultation. Begin telemetry or event monitoring. Add ATG or tacrolimus if no improvement is seen.
Grade 4	Permanently discontinue nivolumab or nivolumab and ipilimumab therapy.
* Including CHF, LV systolic dysfunction, Myocarditis, CPK elevation, and troponin. ** Patients with evidence of myositis without myocarditis may be treated according to "other event." <u>Note:</u> The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

Endocrine (Hypophysitis, Adrenal Insufficiency, Type 1 Diabetes)	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab and Ipilimumab
≤ Grade 1	No change.	No change.
Grade 2-3	Hold until ≤ grade 1 and patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks.	Hold both drugs until ≤ grade 1 and patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Note: Symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered a grade 3 event. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Evaluate pituitary function before beginning steroid therapy or hormone replacement therapy of any kind. Note: Patients with thyroiditis may be re-treated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid hormone replacement. Recommended management: See Endocrinopathy Management Algorithm.		

Nephritis (Creatinine Increased*)	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change.	No change.
Grade 2-3	Hold until ≤ grade 1, then resume.	Hold both drugs until ≤ grade 1, then resume.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue both drugs.
* Rule out noninflammatory (non-immune-mediated) causes. If cause is non-inflammatory, treat accordingly and continue immunotherapy. Patients with fever should be evaluated as clinically appropriate. Isolated fever may occur during infusion reactions or up to several days after infusion. Evaluate over 1-2 weeks for other autoimmune events that may present as fever. Recommended management: See Renal AE Management Algorithm.		

Infusion/ Hypersensitivity reactions*	Management/Next Dose for Nivolumab and Nivolumab plus Ipilimumab
≤ Grade 1	Remain at bedside and monitor patient until symptoms recover. 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 rate. Monitor patient closely. The following pre-medications are recommended at least 30 minutes before future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325-1000 mg. Slowing the infusion rate as above is also recommended.
Grade 2	Stop infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325-1000 mg; remain at bedside and monitor patient until symptoms resolve. Corticosteroid (*e.g.* hydrocortisone 50-100 mg) and/or bronchodilator therapy may also be administered as appropriate if reaction is severe or patient does not respond to diphenhydramine or acetaminophen. When symptoms resolve, restart infusion at 50% of the original rate; 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, then no further drug should be administered at that visit. Administer diphenhydramine 50 mg IV, remain at bedside, and monitor the patient until symptoms resolve. The amount of study drug infused must be recorded on the CRF. The following prophylactic pre-medications are recommended at least 30 minutes before future study drug administrations: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325-1000 mg. If those are not sufficient to prevent infusion reactions, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used.

Infusion/ Hypersensitivity reactions*	Management/Next Dose for Nivolumab and Nivolumab plus Ipilimumab
Grade 3 or 4	Immediately discontinue infusion. Begin an IV infusion of normal saline and treat the patient as follows: • Bronchodilators (recommended) such as epinephrine 0.2-1 mg of a 1:1000 solution for subcutaneous administration or 0.1-0.25 mg of a 1:10,000 solution injected slowly for IV administration; • diphenhydramine 50 mg IV; • methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Permanently discontinue nivolumab therapy in patients on nivolumab and permanently discontinue both ipilimumab and nivolumab in patients on the combination. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery. In case of late-occurring hypersensitivity symptoms, symptomatic treatment may be given (*e.g.*, oral antihistamine or corticosteroids).
* Manifestation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, and bronchospasm. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Study Chair or co-Chair AND reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines. <u>Note:</u> Treatment guidelines may be modified based local institutional standards, as appropriate.	

Fever	Management/Next Dose for Nivolumab Monotherapy	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	Evaluate and continue nivolumab therapy.	Evaluate and continue both drugs.
Grade 2-3	Hold until ≤ grade 1, then resume nivolumab.	Hold both drugs until ≤ grade 1, then resume both drugs.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue both drugs.
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. Also consult the guidelines for infusion reactions, above.		

All Other Events	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
≤ Grade 1	No change in dose.	No change in dose.

All Other Events	Management/Next Dose for Nivolumab	Management/Next Dose for Nivolumab plus Ipilimumab
Grade 2	Hold nivolumab until ≤ grade 1 or baseline (exceptions as noted below) then resume nivolumab.	Hold both drugs until ≤ grade 1 or baseline (exceptions as noted below), then resume both drugs.
Grade 3	Hold nivolumab until ≤ grade 1 or baseline, then resume nivolumab.	Permanently discontinue ipilimumab. Hold nivolumab until ≤ grade 1 or baseline, then resume nivolumab alone.
Grade 4	Permanently discontinue nivolumab therapy.	Permanently discontinue nivolumab and ipilimumab therapy.
Recommended management: As clinically indicated.		

If a patient has any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued study drug dosing should go off protocol treatment.

If a patient has any grade 3 or 4 drug-related laboratory abnormality (except those mentioned above) or electrolyte abnormality, that can be managed indecently from the underlying organ pathology with electrolyte replacement, hormone replacement, insulin, or that does not require treatment does not require discontinuation.

If treatment is delayed >6 weeks for an AE, nivolumab or nivolumab and ipilimumab therapy should be permanently discontinued.

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 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

Patients requiring more than two dose delays for the same event should permanently discontinue nivolumab or nivolumab and ipilimumab therapy.

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.

Doses may be delayed for evaluation and patients may resume 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 2-week observation period without further symptoms at the discretion of the treating investigator.

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 10.1.

[redacted]

Storage: Store intact bottles at controlled room temperature 20-25 °C (68-77 °F).

If a storage temperature excursion is identified, promptly return XL184 (cabozantinib) to 20-25 °C (68-77 °F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing is on-going.

XL184 (cabozantinib) must be dispensed in original bottles. However, repackaging XL184 (cabozantinib) for a short period of time is acceptable and limited to:

- Up to 24 hours when dispensed in an open container such as a pill cup.
- Up to 7 days when dispensed in a closed container (e.g., a pharmacy dispensing bottle).

Route of Administration: Oral.

Method of Administration: Take XL184 (cabozantinib) on an empty stomach; *i.e.*, do not eat 2 hours before and 1 hour after each dosing. Take the dose with a full glass of water at approximately the same time each day. Do not crush or chew. Do not take a missed dose within 12 hours of the next dose.

Potential Drug Interactions:

CYP450 isozymes:
In vitro, XL184 (cabozantinib) is a substrate of CYP3A4 and a weak substrate of CYP2C9. In healthy volunteers, XL184 (cabozantinib) 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, rifapentine, phenobarbital, and St. John's Wort while taking XL184 (cabozantinib). 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 have been on stable doses of XL184 (cabozantinib), as this could significantly increase the exposure to XL184 (cabozantinib).

XL184 (cabozantinib) is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated K_{iapp} = 282 μM) in human liver microsomal (HLM) stability assays. IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 (cabozantinib) 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 (cabozantinib) is an inhibitor of P-glycoprotein transport activity (IC_{50} = 7.0 μM). Co-administration of XL184 (cabozantinib) with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 (cabozantinib) with drugs known to be P-gp substrates (*e.g.*, fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, *etc.*).

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

Protein binding:
XL184 (cabozantinib) is highly protein bound (≥99.9%). Use caution when co-administering XL184 (cabozantinib) with medications that are highly protein-bound (*e.g.*, diazepam, furosemide, dicloxacillin, or propranolol). Avoid administration of warfarin with XL184 (cabozantinib) 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 (cabozantinib) plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 (cabozantinib) is allowed.

QTc prolongation:
Use caution when administering XL184 (cabozantinib) 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 (cabozantinib) plasma concentrations. Refer to the protocol for QTcF criteria.

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

Patient Care Implications: Women of childbearing potential must use highly effective contraception while receiving XL184 (cabozantinib) and for 4 months after the last dose.

Breastfeeding is not allowed while on study. Sexually active males must use highly effective contraception while on study and for 4 months after the last dose.

8.1.2 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 PD-1, 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, PD-L1 and 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 dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), 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 (BMS) and distributed by the Pharmaceutical Management Branch (PMB), CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL 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 the 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 the dose is fixed (*e.g.*, 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 kg, the total volume of infusion must not exceed 4 mL 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 2-8 °C (36-46 °F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@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 (up to 25 °C, 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: 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.

8.1.3 Ipilimumab (NSC 732442)

Chemical Name or Amino Acid Sequence: 4 polypeptide chains, 2 identical heavy chains with 447 amino acids and 2 identical light chains consisting of 215 amino acids.

Other Names: Anti-CTLA-4 monoclonal antibody, MDX-010, Yervoy™

Classification: Human monoclonal antibody

M.W.: 147,991 Daltons

Mode of Action: Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation.

Description: Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) with two manufacturing processes—ongoing trials have been using substances manufactured using Process B. New clinical trials will be using ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

How Supplied: BMS supplies Ipilimumab to the DCTD/NCI. Ipilimumab for injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

	Process C
Component	200 mg/ vial[a]
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

a. Includes 2.6 mL overfill.

b. Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

Preparation: Do not shake. Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2-8 °C, 36-46 °F) or at room temperature/room light (up to 25 °C, 77 °F).

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Storage: Store intact vials refrigerated at (2-8 °C, 36-46 °F), protected from light. Do not freeze.

Stability: Shelf-life surveillance of the intact vials is ongoing. Solution as described above is stable up to 24 hours refrigerated at (2-8 °C, 36-46 °F) or at room temperature/ room light (up to 25 °C, 77 °F).

CAUTION: Ipilimumab does not contain antibacterial preservatives. Use prepared IV solution immediately. Discard partially used vials.

Route of Administration: Intravenous infusion over 90 minutes. Do not administer ipilimumab as an IV push or bolus injection.

Method of Administration: A volumetric pump can be used to infuse ipilimumab at the protocol-specific dose(s) and rate(s) via a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron).

Patient Care Implications: Monitor patients for immune-related adverse events, *e.g.*, rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes.

WOCBP should be advised to continue contraception for 3 months following the last dose of Ipilimumab.

Post-marketing surveillance identified a fatal toxic epidermal necrolysis (TEN) event in a patient who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy. Caution should be used when considering the use of ipilimumab in patients who have previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy.

8.1.4 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

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, a “current” password, and active person registration status. 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.

8.1.4.1 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.

8.1.5 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, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.6 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. STATISTICALCONSIDERATIONS

9.1 Study Design/Endpoints

This is a single arm, prospective, two-stage phase 2 study designed to assess initial evidence of efficacy for CaboNivoIpi in patients with RAI-refractory DTC whose cancer has progressed on one prior VEGFR targeted therapy. The primary endpoint is the ORR, defined as the proportion of patients who have had a PR or CR within the first 6 months after initiation of therapy with CaboNivoIpi.

In a phase 2 multicenter, NCI and ITOG-funded prospective phase 2 study of XL184 (cabozantinib) in patients with RAI-refractory DTC, who progressed on prior VEGFR-targeted

therapy (NCI trial 9312, NCT01811212) (Cabanillas *et al.*, 2017), high objective response rates of 40% were noted. Based on this historical data with XL184 (cabozantinib) alone, an ORR of 40% or less would not be of interest (null hypothesis), and an ORR of 70% or more would be considered promising.

Based on these assumptions, this phase 2 evaluation will require a minimum of 10 and a maximum of 24 evaluable patients to detect a true ORR of ≥70% (*vs.* the null hypothesis that the true ORR is ≤40%). This Simon optimal two-stage phase 2 design allows an interim analysis after 10 evaluable patients, with a Type I error rate of 5% and 90% power. In the final analysis, we will consider this treatment regimen promising if we see ≥14 patients with an objective response out of the total 24 evaluable patients accrued. An interim analysis will be performed after 10 evaluable patients are accrued, where if ≥5 of these 10 patients have a response to treatment we will consider this sufficient evidence to continue accrual. Otherwise, if ≤4 respond, this trial will be terminated early. If the true success rate is ≤40% for this treatment regimen (*i.e.* not promising), then we will have a 63% chance of stopping early at the interim analysis.

The proportion of ORR will be calculated as the number of patients who experience a PR or CR divided by the total number of eligible and evaluable patients. Assuming the number of responses is binomially distributed, 95% binomial confidence intervals will also be calculated for the ORR estimate.

This will use a Simon optimal two-stage phase 2 design with up to 24 evaluable patients.

- First stage (n=10 evaluable patients): If five or more responses are observed, accrual will proceed to the second stage.
- Second stage (n=14 evaluable patients): If a total of 14 or more responses are seen (out of all of 24 patients), then CaboNivoIpi treatment will be considered promising.

9.1.1 Definition of Primary Endpoint

Objective response rate (ORR), defined as the proportion of patients who have had a PR or CR within the first 6 months after initiation of therapy with CaboNivoIpi. All enrolled patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

9.1.2 Definition of Secondary Endpoints

- AEs assessed by CTCAE v5.0 of the combination therapy of CaboNivoIpi in patients with RAI-refractory DTC whose cancer progressed after one prior VEGFR-targeted therapy.
- DOR of patients with DTC. DOR is defined as the time from response (PR or CR) to documented progression.
- PFS of patients with DTC. PFS is defined as the time from initiation of therapy to documented progression or death, whichever occurs first.
- OS of patients with DTC. OS is defined as the time from initiation of therapy to death from any cause.

9.1.3 Definition of Exploratory Endpoints

- Tumor mutation status.
- TILs in biopsies taken pre-treatment and after 12 weeks of CaboNivoIpi therapy.
- T cell receptor repertoire in peripheral blood taken pre-treatment, after 2 weeks of XL184 (cabozantinib), after 12 weeks of CaboNivoIpi therapy, and at disease progression.
- T cell receptor repertoire in biopsies taken pre-treatment and after 12 weeks of CaboNivoIpi therapy
- PD-1/PD-L1 expression in the primary/metastatic tumor in biopsies taken pre-treatment and after 12 weeks of CaboNivoIpi therapy.
- PBMCs assayed pre-treatment, after 2 weeks of XL184 (cabozantinib), after 12 weeks of CaboNivoIpi therapy, and at disease progression.
- Circulating MDSCs assayed pre-treatment, after 2 weeks of XL184 (cabozantinib), after 12 weeks of CaboNivoIpi therapy, and at disease progression.

9.2 Sample Size/Accrual Rate

Up to 24 patients, plus 3 additional patients to account for 10% drop-out and/or non-evaluable patients, will be enrolled for a total of 27 patients. Ten patients plus 1 additional patient (to account for drop-out and/or non-evaluable patients) will be enrolled to Stage 1. If the interim efficacy endpoint is met, 14 more patients plus 2 additional patients (to account for drop-out and/or non-evaluable patients) will be enrolled to Stage 2. Estimated accrual rate is 1-2 patients/month.

9.2.1 Sample Size Justification:

The primary endpoint is ORR, with a null hypothesis of 40% vs. a target of 70%. Employing a Simon's optimal 2-stage design, and assuming 90% power and a 0.05 significance level, a total of 24 evaluable patients will be required. Ten patients (plus 1 additional patient to account for drop-out and/or non-evaluable patients) will be initially accrued in the first stage. If at least 5/10 patients respond to therapy, an additional 14 patients (plus 2 additional patients to account for drop-out and/or non-evaluable patients) will be added for a total of 24 evaluable patients. Observation of a response in at least 14/24 patients would be required to warrant further investigation of this drug combination. Overall, we will enroll a total of 27 patients (24 plus 3 additional patients to account for up to 10% attrition over the course of the study due to drop-out and/or non-evaluable for ORR).

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	1	1	0	1	3
White	6	9	1	1	17
More Than One Race	0	0	0	0	0
Total	8	13	1	2	24

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

9.3 Stratification Factors

This is a non-randomized study and therefore no stratification will be performed

9.4 Analysis of Secondary and Exploratory Endpoints

Frequency and severity of AEs and tolerability of the regimen will be collected and summarized by descriptive statistics. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. All patients who have received at least one dose of the therapeutic agents will be evaluable for toxicity and tolerability.

DOR will be defined as the time from response (PR or CR) to documented progression. OS will be defined as time from initiation of therapy to death. Patients who are still alive will be censored at the last follow-up. PFS will be defined as the time from initiation of therapy to the time of progression or death, whichever occurs first. Patients who are still alive without PD will be censored at the last follow-up. Survival will be analyzed using Kaplan-Meier methods, resulting in median survival times with 95% CI.

For the exploratory studies, tumor mutation status will be summarized using frequency and compared between responders and non-responders using chi-square test or Fisher's exact test, whichever is more appropriate. All other exploratory outcomes including tumor infiltrating lymphocytes, T cell receptor repertoire in tumor and peripheral blood, PBMCs, MDSCs, and PD-1/PD-L1 levels, will be described graphically using boxplots or summary measures (*e.g.*,

mean and standard errors) at each time point. We will also explore how changes in these correlative markers may differ based on whether or not the patient achieved a response. To accomplish this, we will utilize different plotting characters and colors for responses *vs.* not in the graphical analyses to help identify potential patterns, and summarize the changes quantitatively between responders and non-responders. The changes in tumor infiltrating lymphocytes, T cell receptor repertoire, shared T cell clones between tumor and peripheral blood, PBMCs, circulating MDSCs, and PD-1/PD-L1 levels will also be compared between responders and non-responders using two sample t-test or Wilcoxon test if the data is not normally distributed. Linear mixed effect models will also be used to examine the association of biomarkers over the time with the response. Potential confounders (patients' demographics and clinical characteristics) may also be included in the models. All analyses with respect to the exploratory endpoints are intended to be hypothesis-generating and descriptive in nature.

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

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

9.5.2 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 meet the eligibility criteria (with the possible exception of those who receive 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.

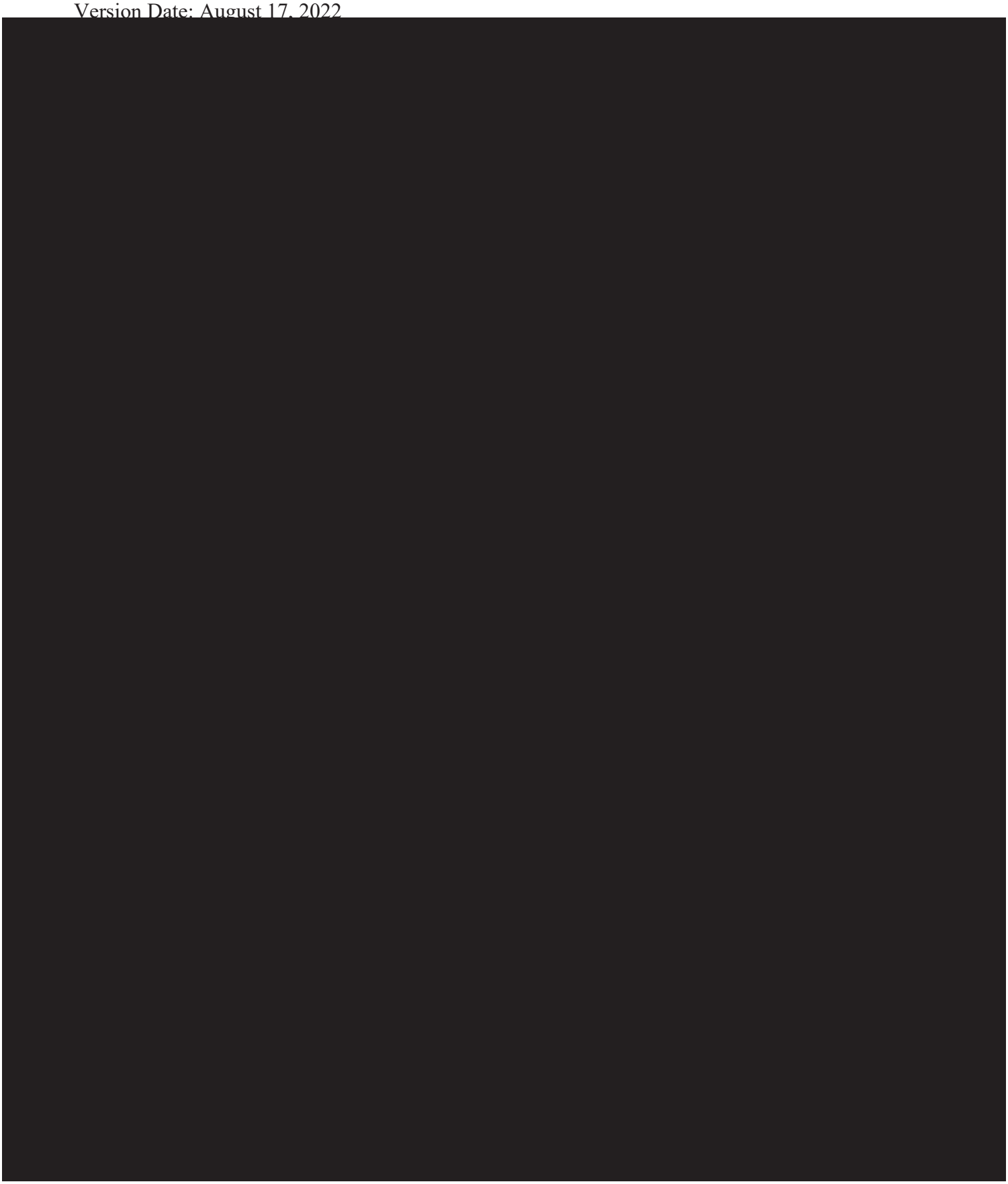
All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, 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.

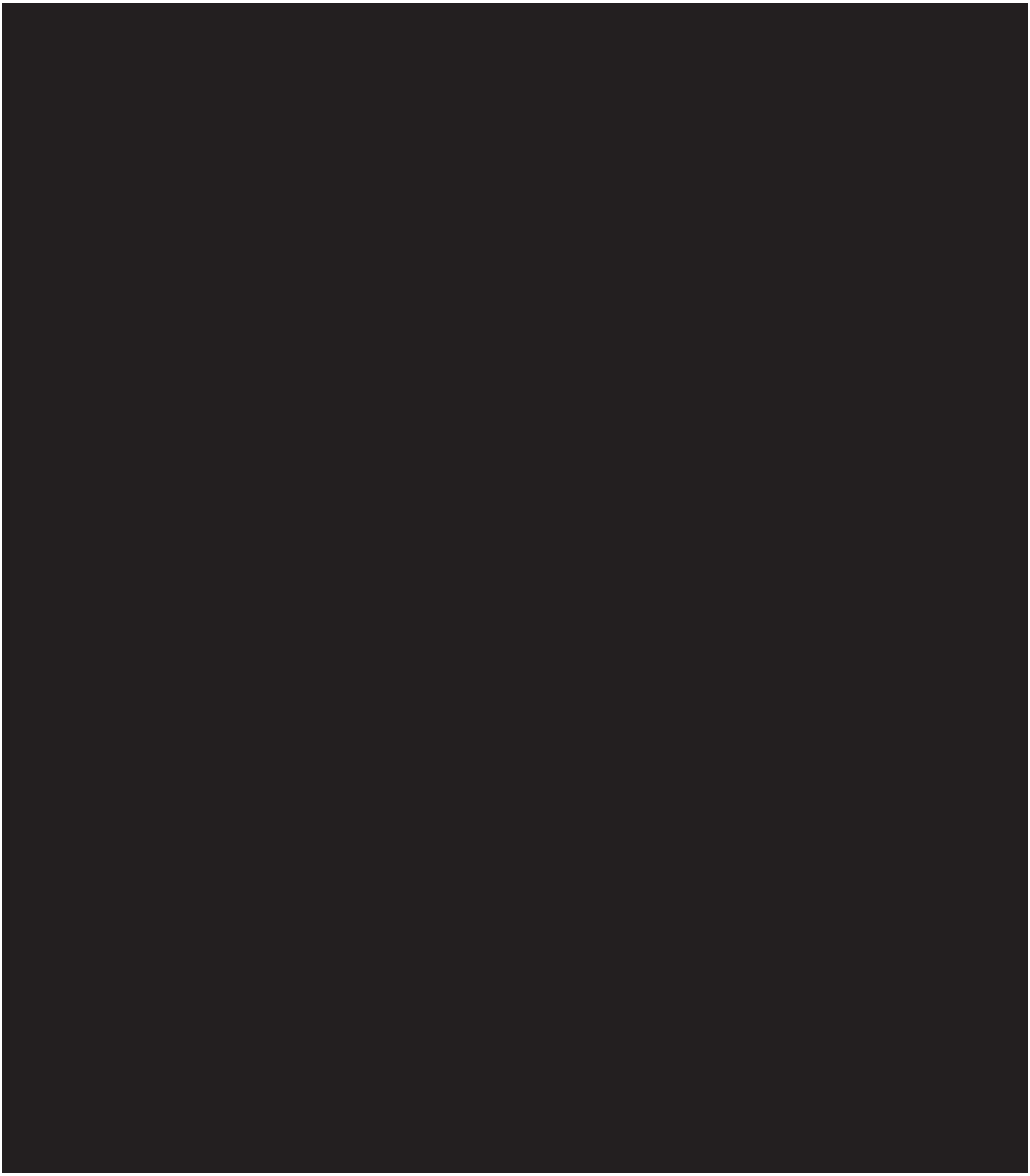
10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

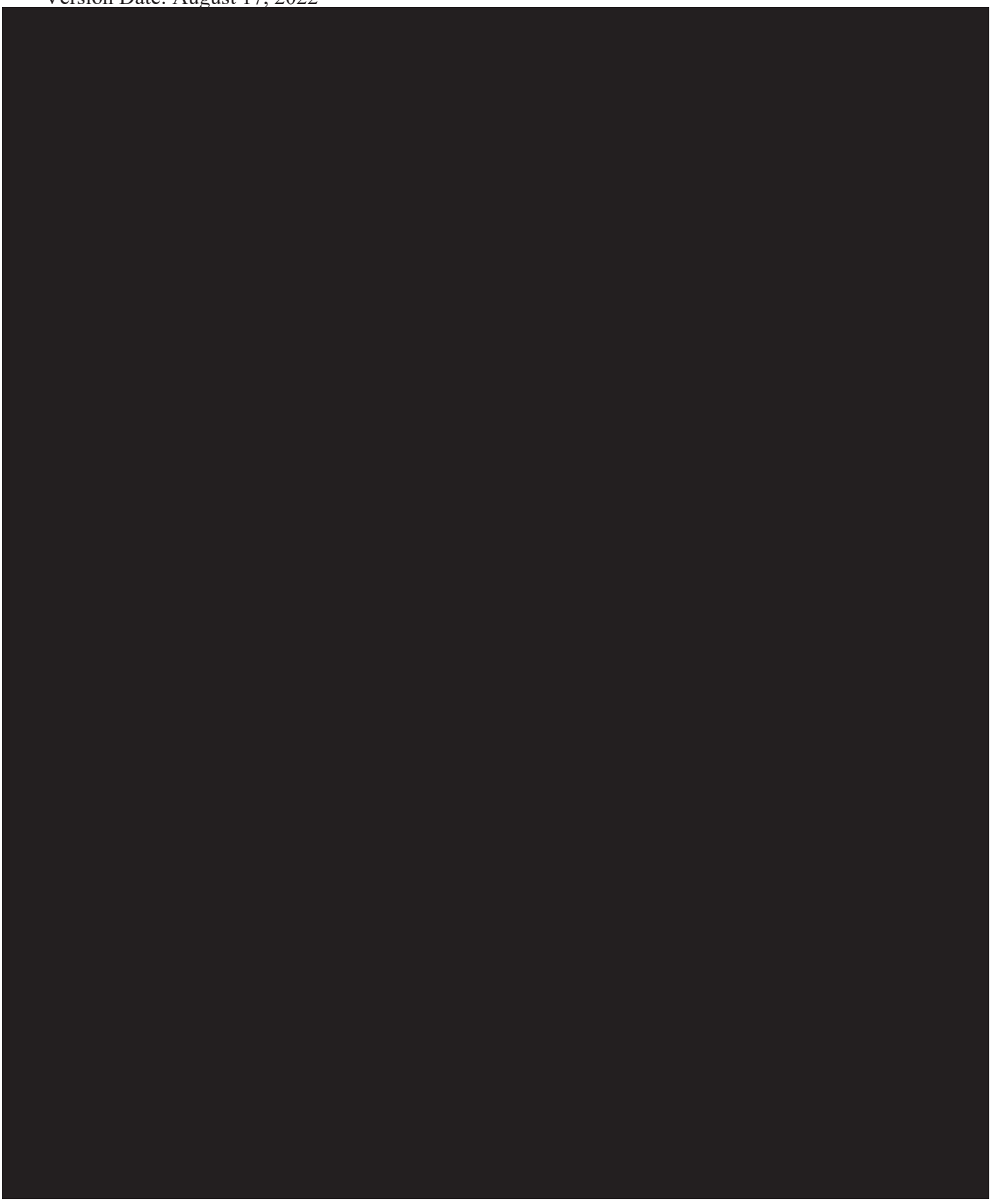
AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting. Adverse Events will be reported in Medidata Rave.

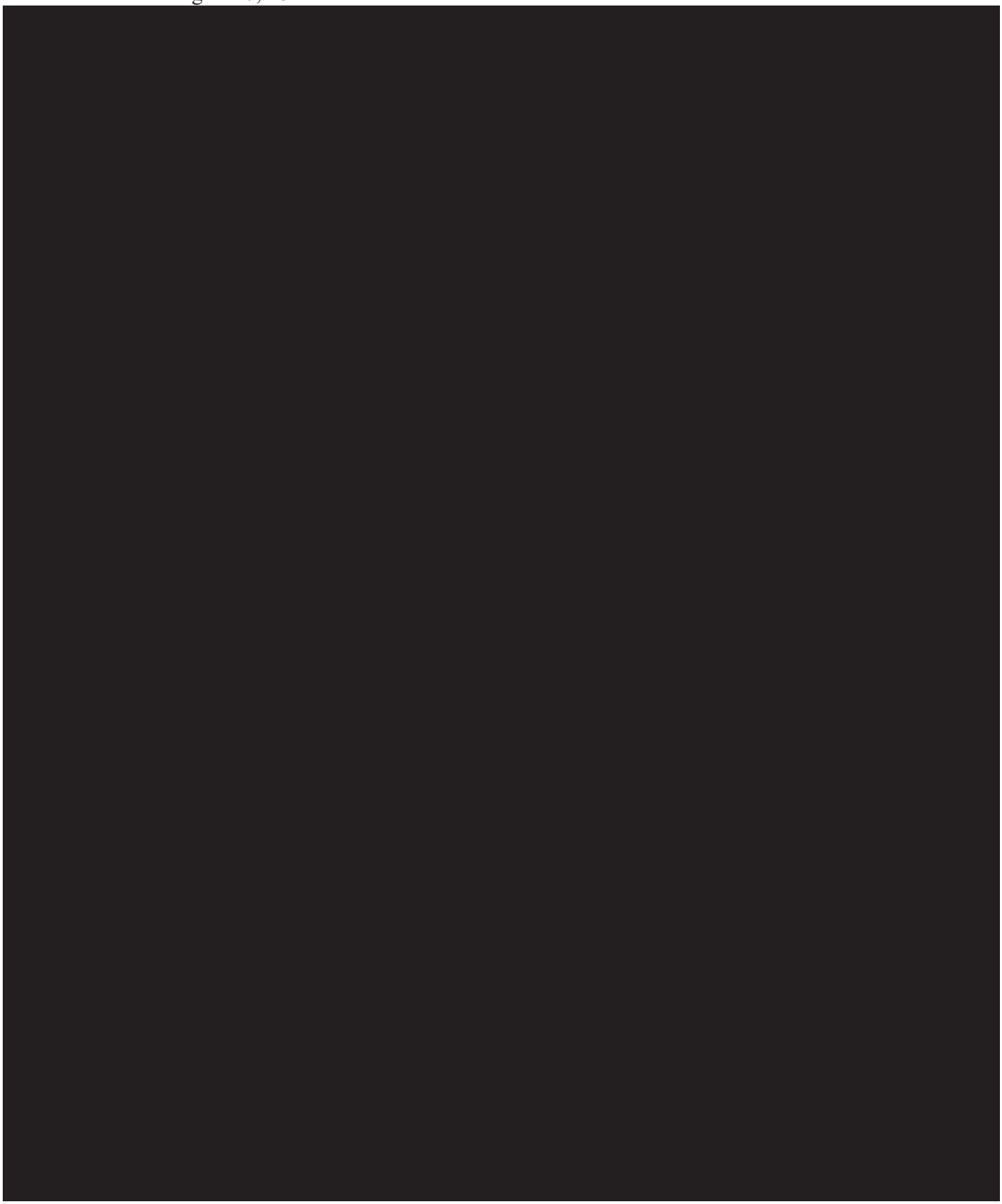
10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

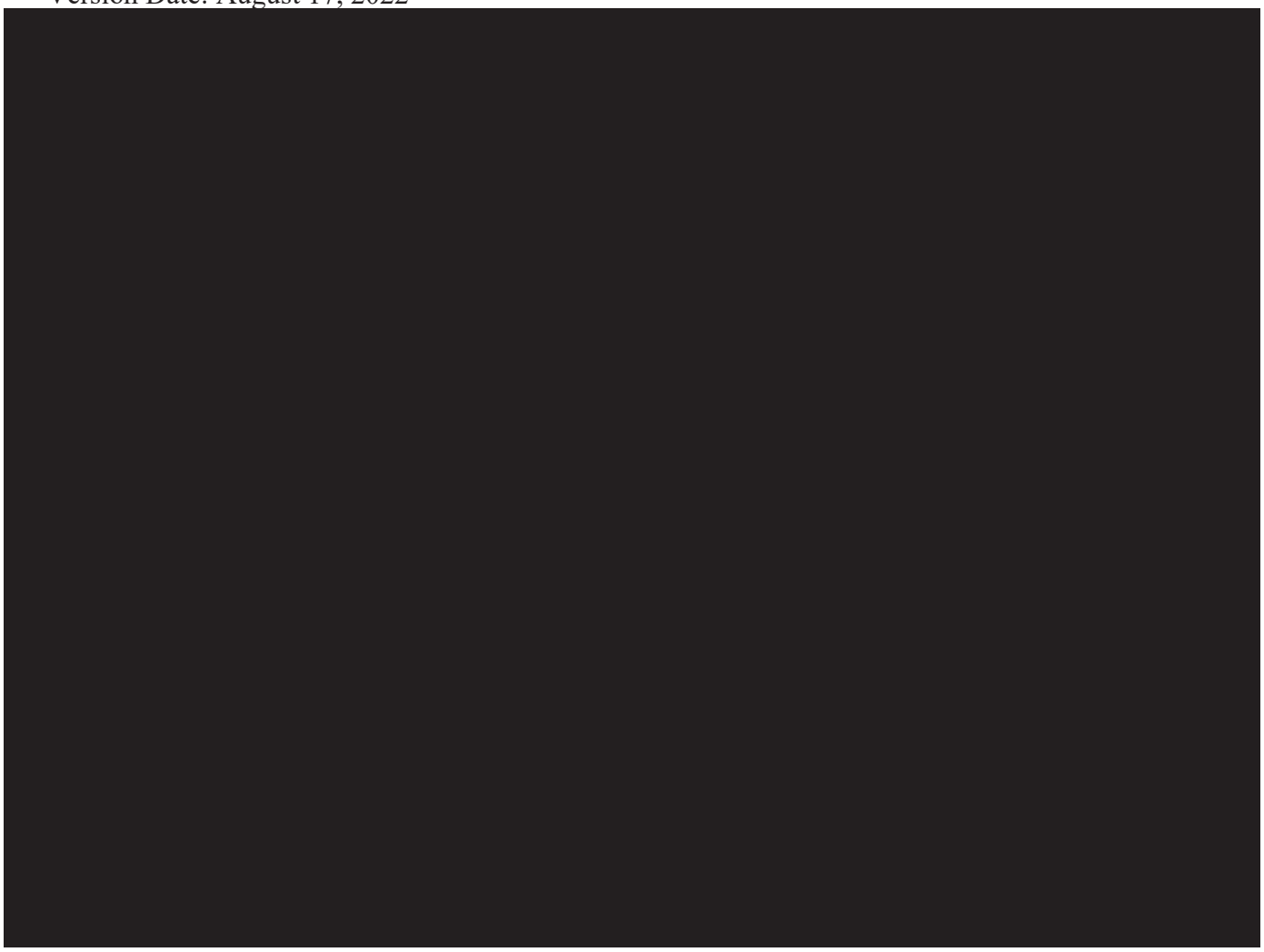
The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to 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.











10.1.2 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, 2020[1]

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		***Anemia (Gr 3)***
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		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***

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%)**	
HEPATOBILIARY 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]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	

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%)**	
		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]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***

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 (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

[2]Pericardial 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.

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

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

[6]Complications 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.

[7]Infusion 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
HEPATOBILIARY 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.

10.1.3 Ipilimumab

Comprehensive Adverse Events and Potential Risks list (CAEPR) for
Ipilimumab (MDX-010, NSCs 732442 and 720801)

Frequency is provided based on 2678 patients. Below is the CAEPR for Ipilimumab (MDX-010).

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 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		*Colitis[2] (Gr 3)*
		Colonic perforation[3]	
	Constipation		
Diarrhea			*Diarrhea (Gr 3)*
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			*Nausea (Gr 3)*

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			*Fatigue (Gr 3)*
	Fever		*Fever (Gr 2)*
		General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic, and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic, and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		*Pruritus (Gr 3)*
Rash maculo-papular			*Rash maculo-papular (Gr 3)*
	Skin and subcutaneous disorders - Other (Sweet's syndrome)		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

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

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage,

Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

Adverse events reported on ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain HEPATOBILIARY
DISORDERS - Hepatic failure[2] IMMUNE SYSTEM
DISORDERS - Allergic reaction INFECTIONS AND
INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010, BMS-734016) 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.

10.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI CTCAE v5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 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 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- 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.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 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.

10.3.3 Expedited Reporting Guidelines

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

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

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." 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 patient 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 hours	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥24 hours	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.

[1] Serious AEs 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

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

Effective Date: May 5, 2011

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

N/A

10.4 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 in Medidata Rave.

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.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS and in Medidata Rave. 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.

10.6 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.

10.7 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.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 30 days prior to registration. Scans must be done within 30 days prior to registration. 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. Scheduled procedures and disease assessments performed every 6 weeks are allowed a window of ±3 days and those performed every 12 weeks are allowed a window of ±7 days. This window should be calculated from the scheduled date of the procedure/assessment.

	Pre-study (≤30 days prior to registration)		Cycles 1 - 4: Cycle length = 6 weeks												Cycles 5+: Cycle length = 4 weeks			
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles 5+			
		Day -14	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	At disease progression	6 weeks after last dose of study drug[D]	Long term follow-up off study treatment[E]
XL184 (cabozantinib)[A]		X→																
Nivolumab[B]			X	X	X	X	X	X	X	X	X	X	X	X	X			
Ipilimumab[C]			X			X			X			X						
Informed consent	X																	
Demographics	X																	
Medical history	X	X	X	X	X	X			X			X			X	X	X	
Concurrent meds	X	X	X	X	X	X			X			X			X	X		
Physical exam	X	X	X	X	X	X			X			X			X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X	X	X	X	X	X			X			X			X	X	X	
Weight	X	X	X	X	X	X			X			X			X	X	X	
Performance status	X	X	X	X	X	X			X			X			X	X	X	
CBC w/differential and platelets	X	X	X	X	X	X			X			X			X	X	X[P]	
Chemistry panel[F]	X	X	X	X	X	X			X			X			X	X	X[P]	
PT/INR, PTT	X															X	X[P]	
Urinalysis	X	X[O]	X	X		X			X			X			X	X	X[P]	
Urine protein to creatinine ratio	X	X[O]	X	X		X			X			X			X	X	X[P]	
Amylase and lipase	X	X[O]	X			X			X			X			X	X	X[P]	
Pregnancy test[G]	X	X	X			X			X			X			X	X		
Serum Tg and Anti-Tg antibody	X	X[O]	X			X			X			X			X	X	X[P]	
Serum TSH and Free T4	X	X[O]	X			X			X			X			X	X	X[P]	
Adrenocorticotropic hormone (ACTH)[H]			X						X						X	X	X[P]	
Serum cortisol (AM measurement preferred)[H]			X						X						X	X	X[P]	
Troponin, 2D echocardiogram, and cardiac history[I]	X																	
EKG[J]	X		X			X			X			X			X	X	X[P]	

	Pre-study (≤30 days prior to registration)	Cycles 1 - 4: Cycle length = 6 weeks													Cycles 5+: Cycle length = 4 weeks			
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles 5+			
		Day -14	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	At disease progression	6 weeks after last dose of study drug[D]	Long term follow-up off study treatment[E]
Adverse event evaluation		X	X	X	X	X			X			X			X	X	X	
Tumor measurements	X								X						X	X		
Imaging[K]	X								X						X[K]	X		
Blood draw for PBMCs, circulating MDSCs, and T-cell clonality assays[L]—Stage 2 only		X	X						X							X		
Archival tissue—Optional, Stage 2 only[M]	X																	
Fresh Tumor Biopsy for correlative studies—Optional, Stage 2 only[N]		X[N]							X[N]									
Phone Follow-up																		X[P]

A: XL184 (cabozantinib): 40 mg PO once daily from Day -14 to Day -1 (run-in) and then every day of Cycle 1 and subsequent cycles.
B: Nivolumab: 240 mg IV on Days 1, 15, and 29 of Cycles 1-4 and 480 mg IV on Day 1 of Cycle 5 and subsequent cycles. May be given ±3 days from a scheduled start of dosing.
C: Ipilimumab: 1 mg/kg IV on Day 1 of Cycles 1-4 (total of four doses). May be given ±3 days from a scheduled start of dosing. When scheduled for the same day, ipilimumab should be given immediately following nivolumab administration.
D: Off-study evaluation.
E: Patients will be followed every 12 weeks after the 6-week visit off study treatment for 2 years after discontinuation of study treatment or until death, whichever occurs first. In addition, patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Follow-up after the 6-week visit may be by phone interview.
F: To include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, GGT, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, and total protein.
G: Serum pregnancy test (women of childbearing potential only) will be performed at least seven days before beginning study therapy. A negative serum or urine pregnancy test is also required at the beginning of each treatment cycle.
H: ACTH and serum cortisol will be tested at C1D1 and C3D1 prior to ipilimumab and nivolumab administration, C5D1 prior to nivolumab administration, and every r other cycle thereafter).
I: Troponin assessment and cardiac history should be obtained at baseline and subsequently as clinically indicated. A 2D echocardiogram should be obtained at baseline for patients with a history of CHF and at the investigator's discretion, and may be repeated as clinically indicated.
J: EKG will be performed at baseline, on Day 1 of Cycles 1 to 5, and then every 8 weeks (every other cycle).
K: CT or MRI scans of neck, chest, abdomen, and pelvis will be done at baseline to assess the response per RECIST v1.1 criteria. CTs or MRIs with IV contrast are encouraged but will be done at the investigator's discretion. CT imaging of neck and chest, abdomen, and pelvis should occur every 12 weeks (±7 days), from C1D1. If the abdomen and pelvis CT scans are negative at baseline, they should be repeated as clinically indicated, however CT imaging of the neck and chest should still occur every 12 weeks (±7 days).
L: Blood for PBMCs, circulating MDSCs, and TCR sequencing should be collected only from patients enrolled to Stage 2. Samples should be collected within three days prior to beginning study therapy on Day -14, within three days prior to beginning nivolumab and ipilimumab on Cycle 1, Day 1, on Cycle 3, Day 1 (±3 days), and at disease progression (±3 days).
M: In patients who consent to archival tissue collection, a request must be placed to the respective pathology department prior to patient registration into the study. Pathology review for specimen adequacy is not needed prior to patient registration.
N: Fresh tumor biopsy is optional and only for patients enrolled to Stage 2 (*i.e.*, the first 11 patients should not have a biopsy done). Biopsy should be collected within five days prior to beginning study therapy on Day -14 and on Cycle 3, Day 1 (±5 days).
O: Do not repeat if done within seven days of Day -14.
P: Should be done if clinically indicated.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CBC=complete blood count, CT=computed tomography, EKG=electrocardiogram, GGT=γ-glutamyl transferase, IV=intravenous, MRI=magnetic resonance imaging, PBMC=peripheral blood mononuclear cell, PO=orally, TSH=thyroid stimulating hormone.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks, with the first response assessment occurring 12 weeks from Cycle 1, Day 1. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST guidelines (version 1.1). 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.

12.1.1 Definitions

12.1.1.1 Evaluable for toxicity

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

12.1.1.2 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.)

12.1.1.3 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.

12.1.2 Disease Parameters

12.1.2.1 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 might or might not be considered measurable.

12.1.2.2 Malignant lymph nodes

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

Non-measurable disease.

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

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

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

12.1.2.3 Target lesions

All measurable lesions up to a maximum of two lesions per organ and five 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.

12.1.2.4 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the five 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.

12.1.3 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.

12.1.3.1 Clinical lesions

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

12.1.3.2 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.

12.1.3.3 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 same 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.

12.1.3.4 PET-CT

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

12.1.3.5 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 to CT, MRI may be used instead of CT in selected instances.

12.1.3.6 Endoscopy and 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 CR or surgical resection is an endpoint.

12.1.3.7 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. 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.

12.1.3.8 Cytology and Histology

These techniques can be used to differentiate between PRs and CRs 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 PD.

12.1.3.9 FDG-PET

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

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

Progressive Disease: 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.

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

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 PI).

12.1.4.3 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 PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 weeks confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

12.1.5 Duration of Response

12.1.5.1 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 PD is objectively documented (taking as reference for PD 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 PD is objectively documented.

12.1.5.2 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.

12.1.6 Progression-Free Survival

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

12.1.7 Response Review

There is no planned central review at this point for this study.

12.2 Other Response Parameters

Overall survival (OS) will be defined as time from study therapy initiation to death. Patients who are still alive will be censored at the last follow-up.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol PI 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 AEs; reporting of expedited AEs; and accumulation of reported AEs from other trials testing the same drug(s). The Protocol PI and statistician have access to the data at all times through the CTMS web-based reporting portal.

The Protocol PI 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 this phase 2 trial will require sign-off by the Protocol PI 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.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this

trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff 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 in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

For studies assigned for CTMS Routine Monitoring:

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every 2 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)-619-7862, or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 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 two 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 four 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 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).

13.3 CTEP Multicenter Guidelines

N/A

13.4 Collaborative Agreements Language

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the patient of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human patients, including, if applicable, the "Standards for Privacy of Individually Identifiable Health Information" set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

Email: ncicteppubs@mail.nih.gov

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

13.5 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all

data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.6 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

13.7 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

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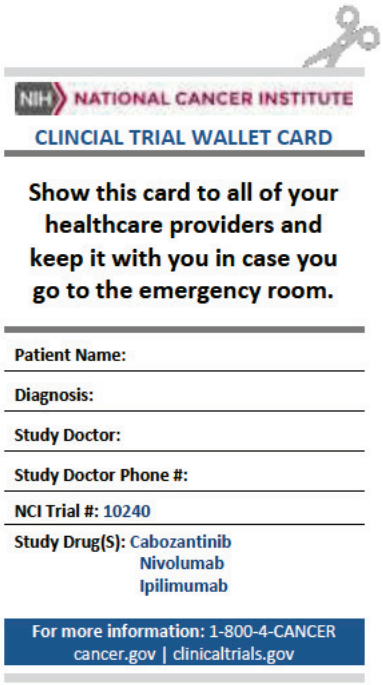
APPENDIX A. PERFORMANCE STATUS CRITERIA

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

APPENDIX B. PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINCIAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10240

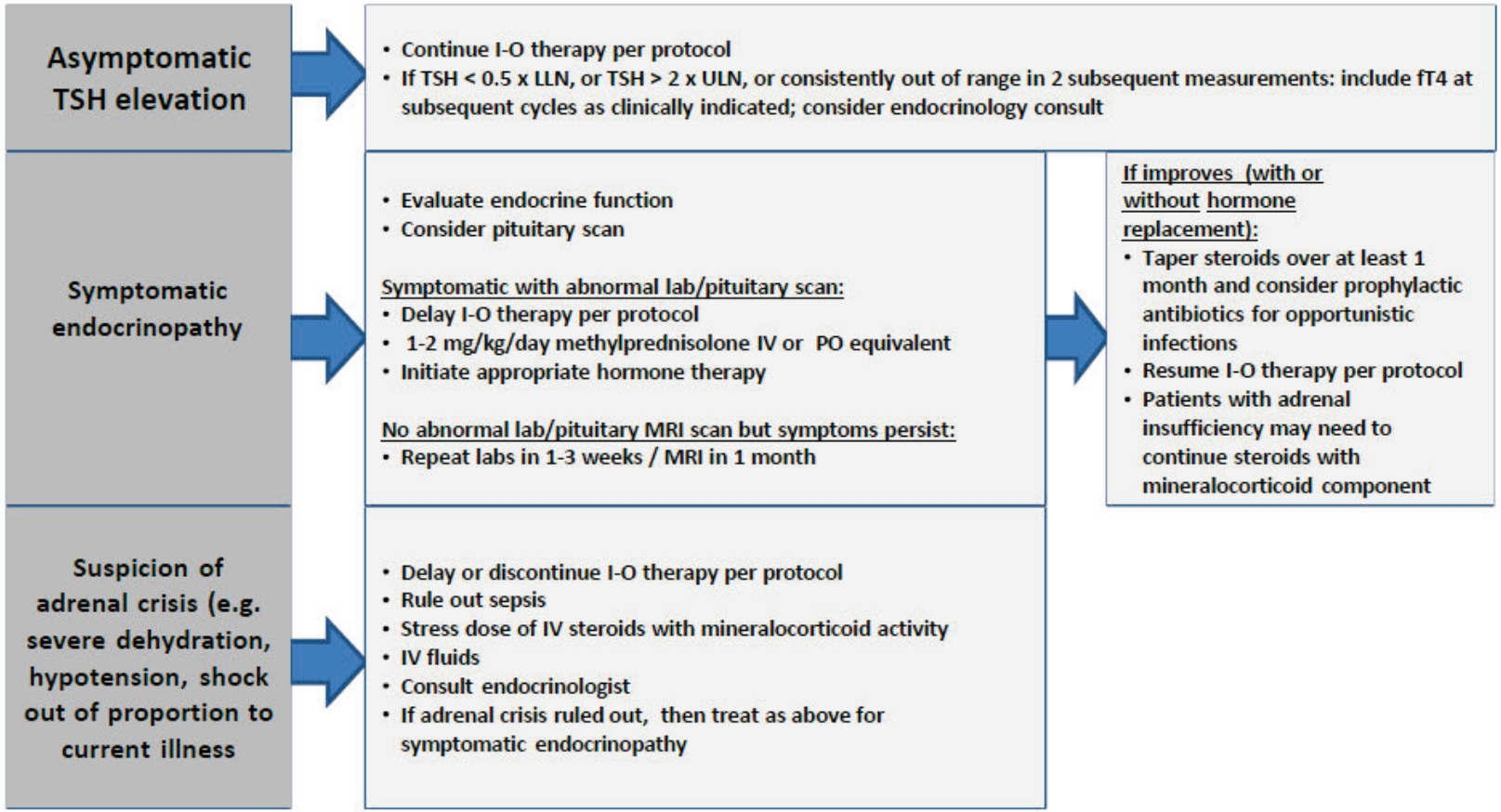
Study Drug(S): Cabozantinib
Nivolumab
Ipilimumab

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX C. NIVOLUMAB AND IPILIMUMAB MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, MYOCARDITIS, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Adverse Event Management Algorithm

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

GI Adverse Event Management Algorithm

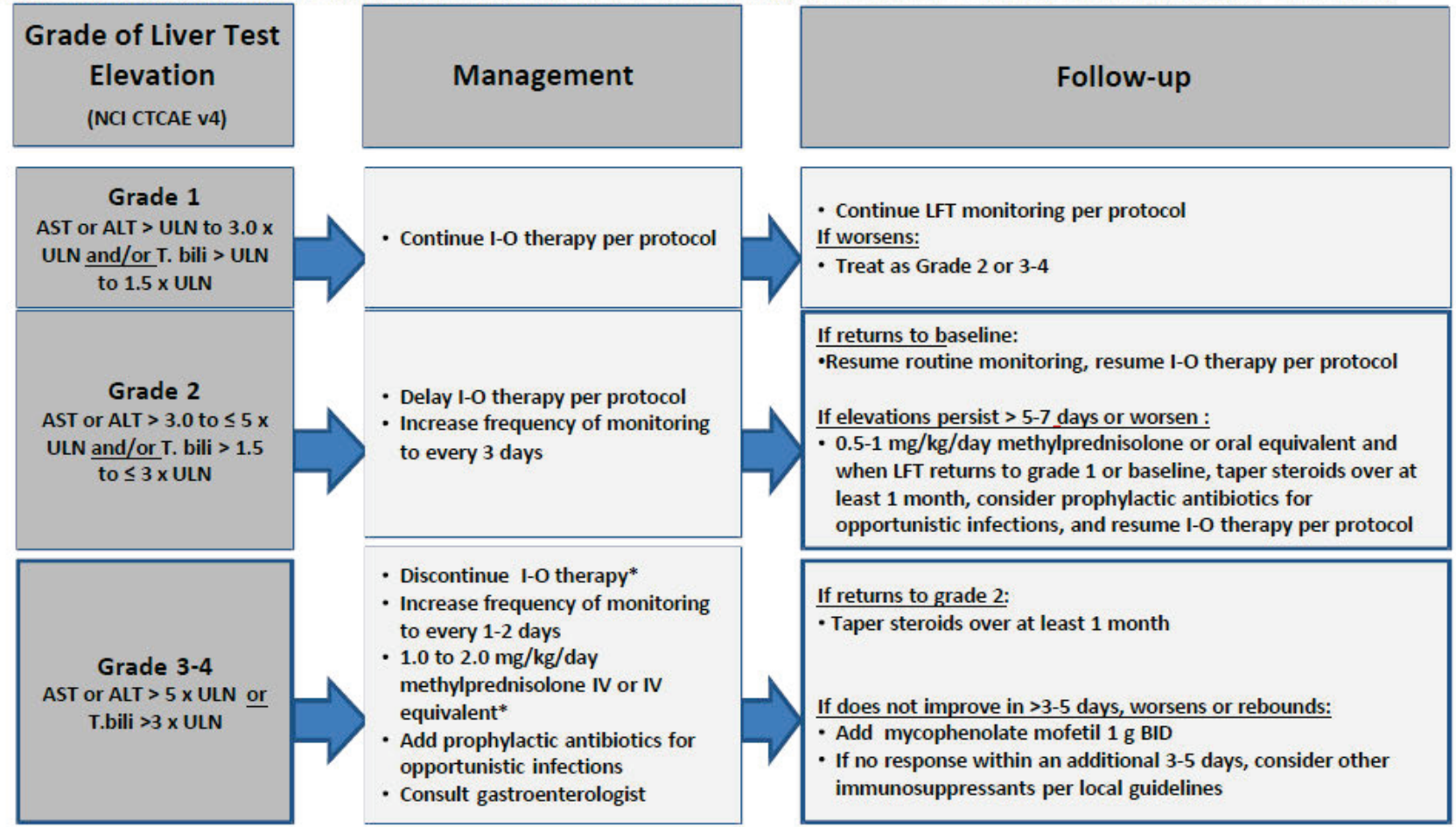
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

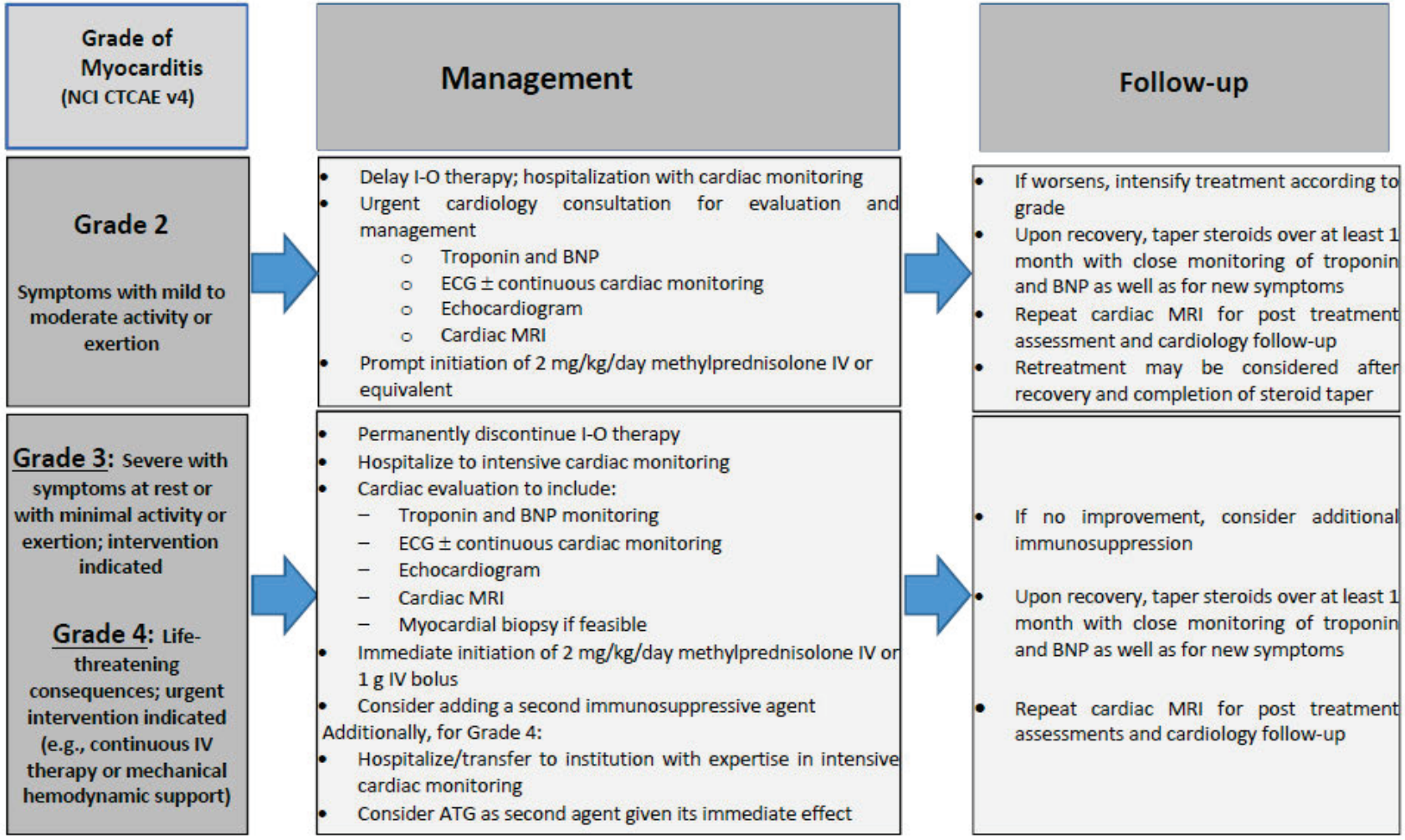
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



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.

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

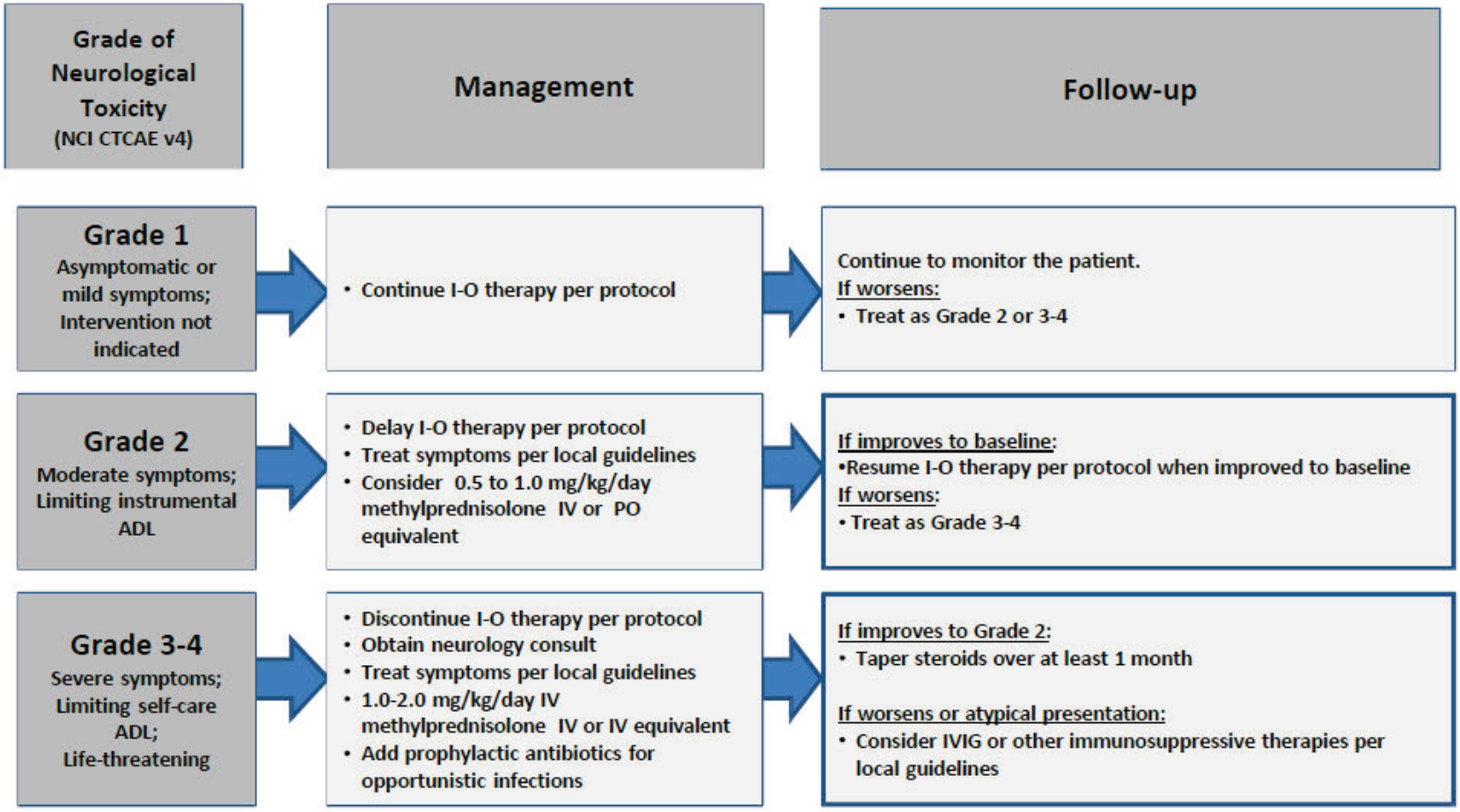
Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

Neurological Adverse Event Management Algorithm

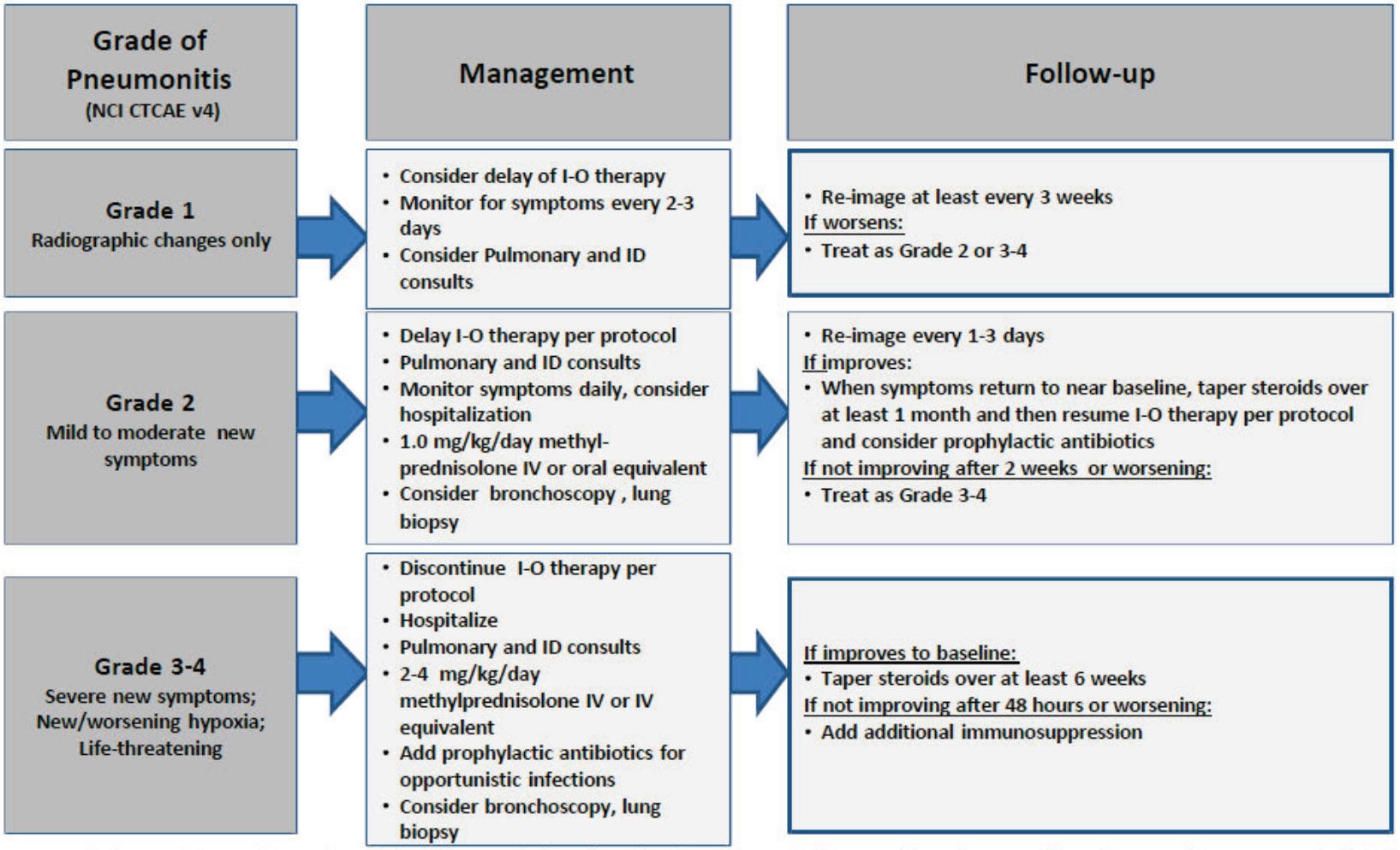
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

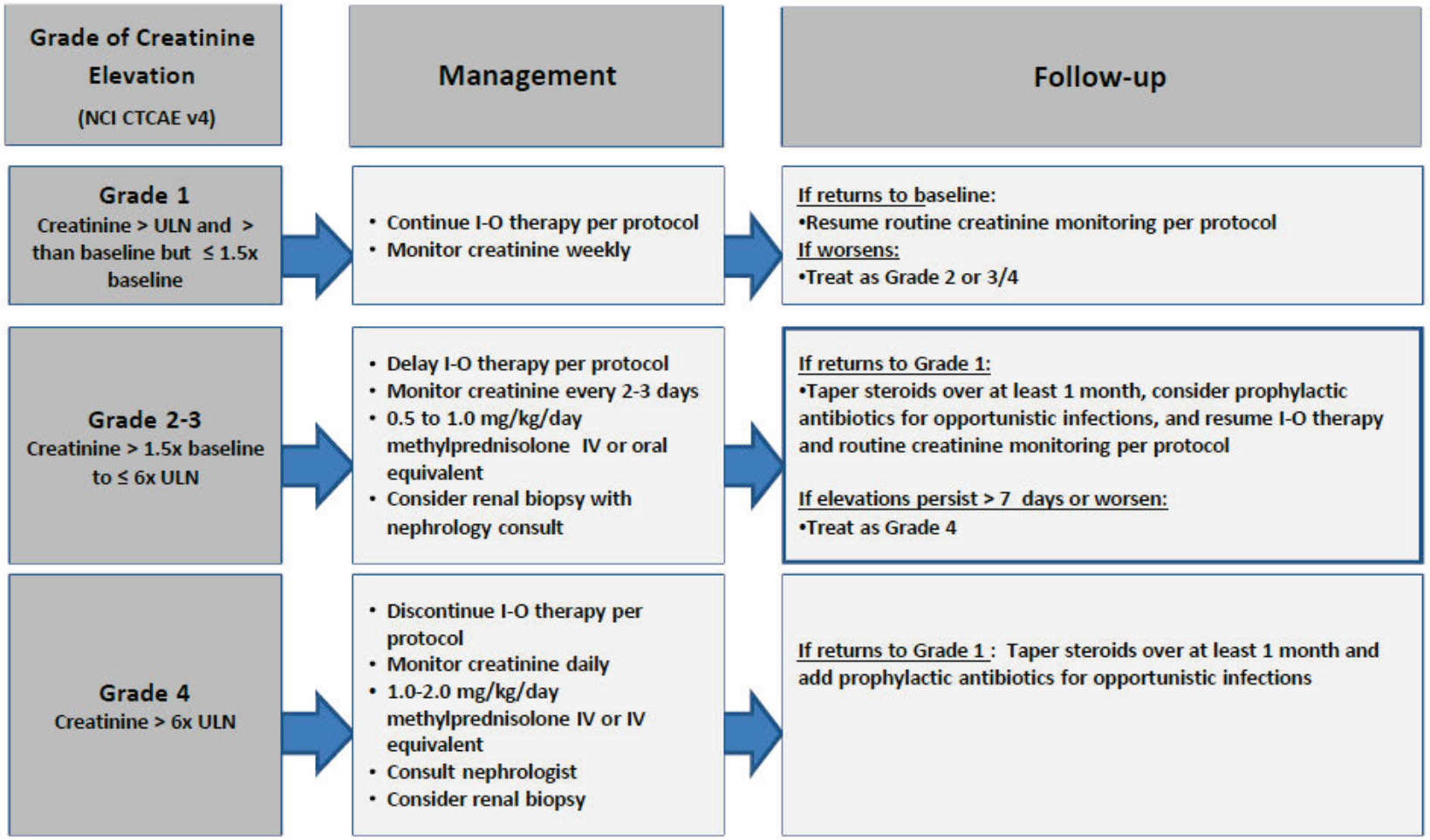
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

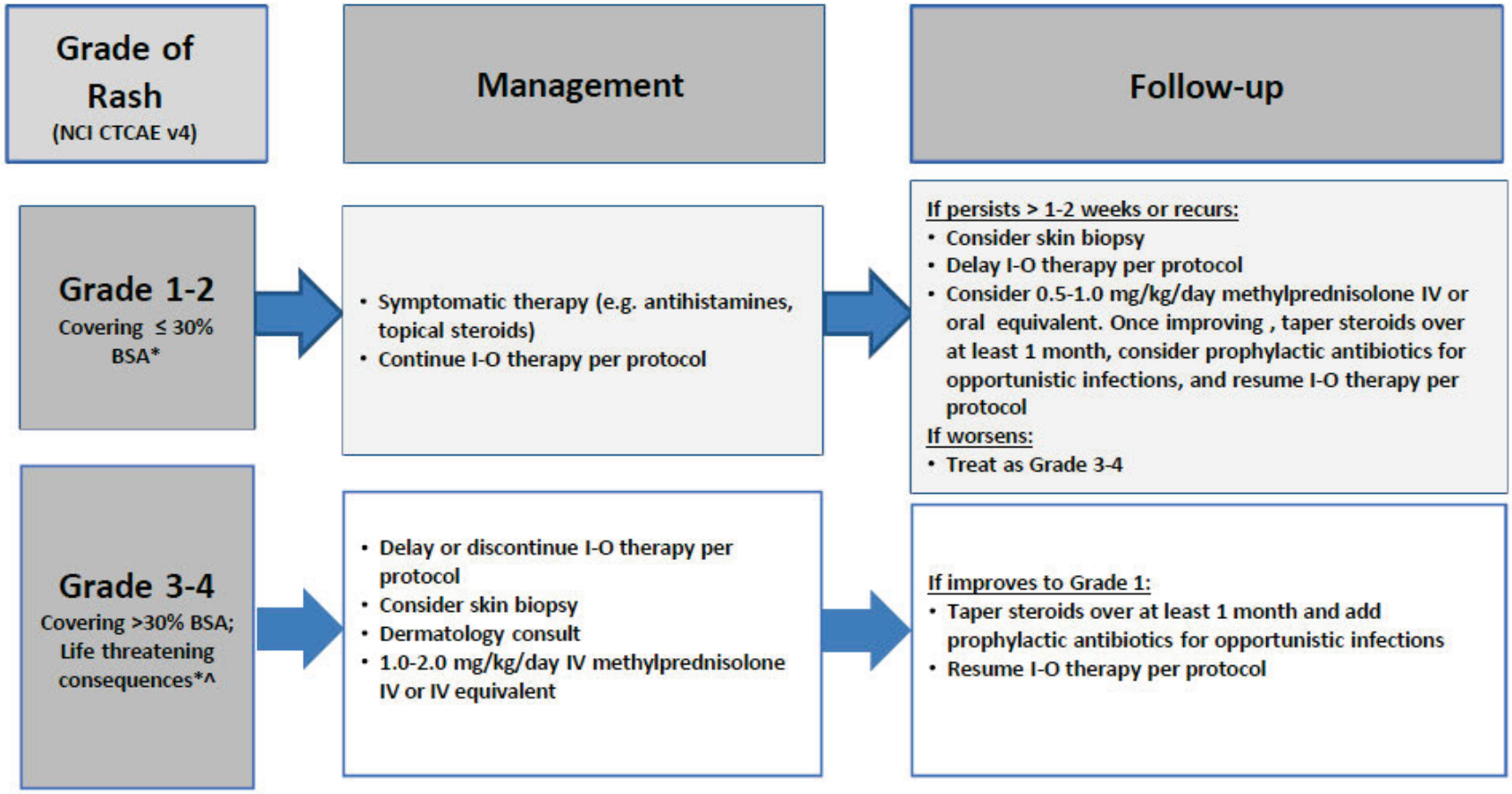
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

APPENDIX D. MEDICATION DIARIES

D.1 Medication Diary for XL184 (cabozantinib) – Days -14 to -1

CTEP-assigned Protocol # 10240
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – XL184 (cabozantinib)

Today's date:_____ Agent: XL184 (cabozantinib)_____**mg**

Patient Name:_____(*initials acceptable)* Patient Study ID: _____

INSTRUCTIONS TO THE PATIENT:

1. You will take your dose of XL184 (cabozantinib) once daily, and you should take your dose at the same time of day each day. You will take two 20 mg tablets every day. You should swallow the tablets as a whole. Do not crush or chew. You should take XL184 (cabozantinib) on an empty stomach, and at least 2 hours after and 1 hour before eating.
2. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by patients taking XL184 (cabozantinib).
3. Record the date, the number of tablets you took, and when you took them.
4. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 12 hours of the scheduled time. If it is more than 12 hours after the scheduled time, do not take the missed dose. Take your next dose at the regularly scheduled time.
5. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
6. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1.				
2.				
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6.				
7.				
8.				
9.				
10.				
11.				
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14.				

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature: _____

D.2 Medication Diary for XL184 (cabozantinib) – Cycles 1-4

CTEP-assigned Protocol # 10240
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – XL184 (cabozantinib)

Today's date:_____ Agent: XL184 (cabozantinib)_____**mg**

Patient Name:_____(*initials acceptable)* Patient Study ID: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of XL184 (cabozantinib) once daily, and you should take your dose at the same time of day each day. You will take two 20 mg tablets every day. You should swallow the tablets as a whole. Do not crush or chew. You should take XL184 (cabozantinib) on an empty stomach, and at least 2 hours after and 1 hour before eating.
3. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by patients taking XL184 (cabozantinib).
4. Record the date, the number of tablets you took, and when you took them.
5. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 12 hours of the scheduled time. If it is more than 12 hours after the scheduled time, do not take the missed dose. Take your next dose at the regularly scheduled time.
6. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of tablets taken	Comments
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INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of XL184 (cabozantinib) once daily, and you should take your dose at the same time of day each day. You will take two 20 mg tablets every day. You should swallow the tablets as a whole. Do not crush or chew. You should take XL184 (cabozantinib) on an empty stomach, and at least 2 hours after and 1 hour before eating.
3. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by patients taking XL184 (cabozantinib).
4. Record the date, the number of tablets you took, and when you took them.
5. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 12 hours of the scheduled time. If it is more than 12 hours after the scheduled time, do not take the missed dose. Take your next dose at the regularly scheduled time.
6. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of tablets taken	Comments
29.				
30.				
31.				
32.				
33.				
34.				
35.				
36.				
37.				
38.				
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Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature: _____

D.3 Medication Diary for XL184 (cabozantinib) – Cycles 5+

CTEP-assigned Protocol # 10240
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – XL184 (cabozantinib)

Today's date:_____ Agent: XL184 (cabozantinib)_____**mg**

Patient Name:_____(*initials acceptable)* Patient Study ID: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of XL184 (cabozantinib) once daily, and you should take your dose at the same time of day each day. You will take two 20 mg tablets every day. You should swallow the tablets as a whole. Do not crush or chew. You should take XL184 (cabozantinib) on an empty stomach, and at least 2 hours after and 1 hour before eating.
3. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by patients taking XL184 (cabozantinib).
4. Record the date, the number of tablets you took, and when you took them.
5. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 12 hours of the scheduled time. If it is more than 12 hours after the scheduled time, do not take the missed dose. Take your next dose at the regularly scheduled time.
6. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1.				
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Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature: _____

APPENDIX E. TISSUE BIOPSY VERIFICATION

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

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

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

Please have the Clinician* 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): Archival Primary / Archival Metastatic or Fresh Primary / Fresh Metastatic

Time point (circle one): Pre-Study Day -14 Cycle 3 Day 1

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.

_____ _____

Clinician Signature Date

_____

Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

Version: 1
Effective Date: 9/2019