SUMMARY OF CHANGES – Protocol

For Protocol Amendment #: 16

NCI Protocol #: 10387
Local Protocol #: 2020-12258

NCI Version Date: 04/10/24
Protocol Date: 04/10/24

The summary of changes table below provides a detailed summary and rationale for all changes to protocol #10387, from Protocol Version 08/24/23 to Protocol Version 04/10/24.

#	Section	Comments
1.	**11. Study Calendar**	Add more details regarding the KS assessment as below: For patients with KS, the Baseline KS Assessment will be completed by the treating physician within 4 weeks prior to start of protocol therapy. Beginning C1D1 and onward, participants will be evaluated using the Overall KS Response Assessment every 8 weeks (+/- 4 weeks) until the off-study visit
2.	**Regulatory Coordinator**	Regulatory Coordinator role has been updated to oversee protocol compliance with regulatory requirements.
3.	**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**	The Adverse Event Reporting Requirements section have been updated to reflect the new requirements that are effective from August 30, 2024

NCI Protocol #: 10387

Local Protocol #: 2020-12258

ClinicalTrials.gov Identifier: NCT04514484

TITLE: Pilot Trial of Nivolumab plus Cabozantinib for Advanced Solid Tumors in Patients with HIV infection

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LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

NCI Protocol#: 10387
Version Date: April 10, 2024

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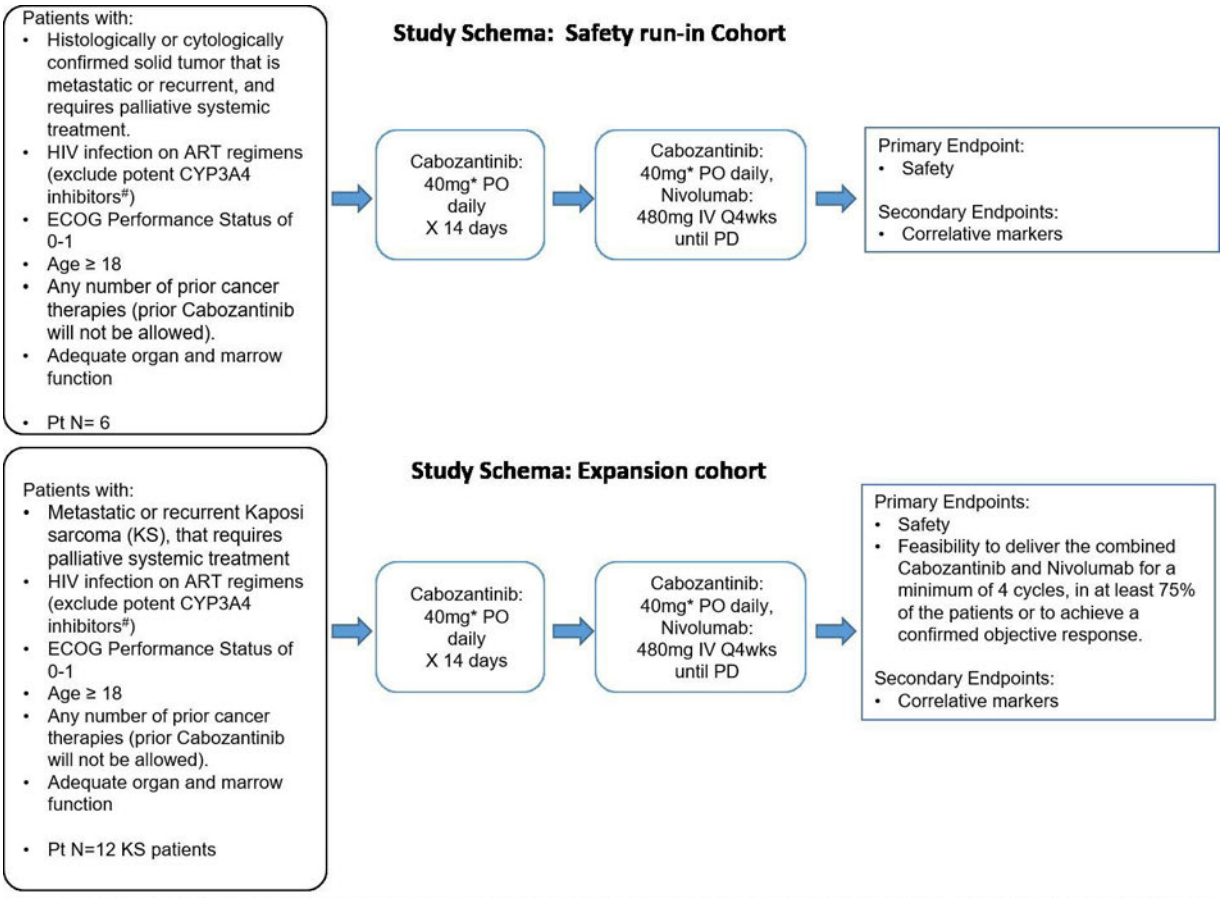
NCI-Supplied Agent(s): XL184 (Cabozantinib) (NSC761968)
Nivolumab (BMS-936558, MDX-1106) (NSC748726)

IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / March 6, 2020
Revision 1 / May 14, 2020
Revision 2 / June 11, 2020
Revision 3 / July 7, 2020
Revision 4a / August 27, 2020
Revision 5 / September 29, 2020
Revision 6 / February 4, 2021
Revision 7 / March 17, 2021
Revision 8 / June 1, 2021
Revision 9/ August 30, 2021
Revision 10 / October 13, 2021
Revision 11 / April 14, 2022
Revision 12 / June 10, 2022
Revision 13 / August 3, 2022
Revision 14 / August 18, 2022
Revision 15 / August 24, 2023
Revision 16/ April 10, 2024

SCHEMA



*Although unlikely based on the data from previous and ongoing studies, a dose reduction (-1 dose level) at 20mg daily Cabozantinib for the first 6 patients in the run-in phase is permitted, and the subsequent dose at the expansion cohort will be adjusted accordingly.
#Potent CYP3A4-inhibiting retrovirals: such as ritonavir or cobicistat-boosted ART regimens, which may have potential interaction leading to higher drug levels of Cabozantinib.

Safety Run-In and Expansion Cohort Treatment Regimen

Agent	Dose	Route	Schedule	Cycle Length
Cabozantinib	40mg	PO, QD	Day -14 to -1	14-day Run-in/priming period
Cabozantinib	40mg	PO, QD	Day 1-Day 28	28 Days
Nivolumab	480mg	IV, Q4W	Day 1	
PO = orally; IV = intravenously; QD = every day; Q4W = every 4 weeks				

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the safety of combined nivolumab and XL184 (cabozantinib) in human immunodeficiency virus (HIV) patients with advanced solid tumors.

1.1.2 To determine the feasibility to deliver the combined nivolumab and XL184 (cabozantinib) for a minimum of 4 cycles in at least 75% of the subjects in the expanded cohort with Kaposi Sarcoma (KS) or to achieve a confirmed objective response.

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity in subjects with KS. Although the clinical benefit of the combination of these drug in this patient population has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the subject will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 To assess the effect of treatment on participants' immune status (CD4 and CD8 cell counts) and HIV viral loads.

1.2.3 To preliminarily evaluate the objective response rate (ORR) to the combination treatment in subjects with KS.

1.3 Exploratory Objectives

1.3.1 To assess duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in subjects with KS.

1.3.2 To assess the PD-L1 IHC status in tumors and tumor microenvironment and its association with clinical outcome.

1.3.3 To assess the expression characteristics and cellular distribution of immune checkpoints (PD-L1, B7x, HHLA2, B7H3), infiltrating immune cells (CD4 T cells, CD8 T cells, Treg, MDSC), and other tumor microenvironment biomarkers (VEGF, VEGFR, MET, and AXL) in the tissue by MQIF. Determine the association between these expression profiles and clinical outcomes.

1.3.4 To correlate markers of immune activation and expansion of immune cell subsets and cytokines with clinical outcomes.

1.3.5 To assess the treatment effects on latent HIV reservoir.

1.3.6 To investigate the dynamic changes of immune checkpoints, angiogenesis markers, and infiltrating immune cells among subjects with available pre- and post-treatment biopsy

samples [including subjects with Kaposi Sarcoma (KS)].

2. BACKGROUND

2.1 Study Disease

There are approximately 1.1 million patients with HIV infection in the US. Malignancies are observed in excess among them, including both AIDS-defining malignancies (ADMs) and non-AIDS defining cancers (NADCs) (U.S Statistics. HIV.gov, 2019; Ikeda et al., 2014). The former includes KS, non-Hodgkin's lymphoma, and cervical cancer. With wide use of antiretroviral therapy (ART), the development of ADMs has declined, however, the risk of NADCs (such as anal cancer, lung cancer, head and neck cancer, and hepatocellular carcinoma) has increased and become much more common among this population (Ikeda et al., 2014; Shiels et al., 2011). Historically, cancer patients with HIV infection have been excluded from many clinical trials and remain largely understudied. At the same time, potential drug interaction between ART and certain cancer treatment (such as agents modulating the cytochrome P450 [CYP] 3A4 system) has raised tolerability and activity concerns that require close monitoring.

The Montefiore Medical Center has the largest HIV program in New York City. Over the past 5 years, 667 cases of newly diagnosed solid tumors were identified in HIV-infected patients from Montefiore. Recently, one of the largest experiences among patients with HIV infection and lung cancer (n=178) (Attarian et al., 2019) was compiled at Montefiore. Compared to the overallpatient population, lung cancer patients with HIV infection at our system presented at a significantly younger age (57 vs. 68 years, p=0.014) and advanced stage (49% vs. 68%, p<0.001). Moreover, this data showed a remarkably low expression of PD-L1 (using 22C3 antibody) in this patient population: The majority (78%) of patients had PD-L1 Tumor Proportion Score (TPS) <1%, whereas only 8% of them had PD-L1 TPS >50%. Among the 11 patients who received immunotherapy (8 single-agent immunotherapy), two (18%) had partial response (PR) and 3 had (27%) SD. No patients had any grade 3 or higher immune adverse events (AEs).

Taken together, focused studies are warranted to study the safety and efficacy of exciting novel anti-cancer agents (such as immunotherapy and molecularly targeted treatment), as well as the underlying biology and immune modulation for this underserved patient population.

2.2 CTEP Agents

2.2.1 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator's Brochure, 2020). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of

nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) ina phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok et al., 2013).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved 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) (Investigator's Brochure, 2020). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that losefunction and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte- activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

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

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody 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 (Investigator's Brochure, 2020).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and 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.

2.2.1.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2020). 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 (Kd) = 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 (MC38) and fibrosarcoma (SAl/N).

2.2.1.2 Clinical Development of Nivolumab

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 80 clinical studies (Investigators Brochure, 2020). Across those studies, approximately 23,507 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies orstudies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti- angiogenics, and targeted therapies. Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), small cell lung cancer (SCLC), esophageal squamous cell carcinoma (ESCC) (approved indications), and other tumor types, as monotherapy or in combination with ipilimumab or other therapeutics. The majority of responses were durable andexceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, subjects with advanced or metastatic NSCLC, subjects with advanced RCC, and subjects with recurrent or metastatic SCCHN.

2.2.1.3 Pharmacokinetics

The PK of nivolumab as monotherapy was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple-doses of nivolumab as a 60-minute infusion every 2 or 3 weeks (Investigator Brochure, 2020). The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks (Q2W). Nivolumab clearance was shown to decrease over time, but this decrease is not considered to be

clinically relevant. The mean terminal elimination half-life of nivolumab is 25 days consistent with the half-life of endogenous IgG4. Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 4-fold. Following nivolumab 360 mg every 3 weeks (Q3W), the steady state maximum concentration is predicted to be approximately 23% higher relative to that following nivolumab 3 mg/kg Q2W; however, the range of exposures across body weights (35 to 160 kg) is predicted to be well below corresponding exposures observed at the well-tolerated dosing regimen of 10 mg/kg Q2W

2.2.1.4 Efficacy

In a phase 1 (1, 3, and 10 mg/kg Nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed atall doses (Sznol et al., 2013). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non- squamous NSCLC, respectively (Brahmer et al., 2013). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year (Drake et al., 2013).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok et al., 2013). The combined treatment was subsequently administered every12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumabreceived nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced- regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi et al., 2013). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

2.2.1.5 Toxicology

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. The safety profile of nivolumab in combination with ipilimumab was consistent with themechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. 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. Across all studies conducted to date, drug- related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine

abnormalities, GI toxicity, dermatologic toxicity (including rash, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN]), hepatotoxicity, and myotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managedsuccessfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies).

2.2.1.6 Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of 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-γ (IFN- γ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

2.2.1.7 Marketing Experience

Nivolumab monotherapy (Opdivo®) was first approved in July 2014 in Japan for unresectable melanoma (Nivolumab Investigator's Brochure, 2020). Since then, it has been approved in multiple countries, including the US, and has been approved for several other indications alone or in combination, including unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic NSCLC, SCLC, advanced RCC, cHL, SCCHN, urothelial carcinoma, HCC, ESCC, and microsatellite high or mismatch repair deficient metastatic CRC. Nivolumab isalso 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.

2.2.2 XL184 (Cabozantinib)

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2019). The primary targets of XL184 are MET and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of XL184 against c-Met and VEGFR2 has been demonstrated in 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, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers.

The RTK MET, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or 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 (Investigator's Brochure, 2019). 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 include: the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of MET by mutation of gene amplification in multiple cancer types; (4) introduction of MET and HGF (or mutant MET) into cell lines, conferred the properties of tumorgenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of MET/HGF function with dominant-negative receptors, antibody antagonists (both MET and HGF), and biologic antagonists (e.g., NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo (Christensen et al., 2005).

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-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 a 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 HCC, and correlated withTNBC (i.e., therapy-resistant) and poor survival.

2.2.2.1 Nonclinical Development of XL184 (cabozantinib)

2.2.2.1.1 Nonclinical In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes et al., 2009). In RIP-Tag2 transgenic mice, tumors treated with XL184 (cabozantinib) were smaller ($P < 0.05$) than in mice treated with vehicle or ananti- VEGF antibody, but were also less invasive ($P < 0.05$) and had no liver metastases (Sennino et al., 2009). All mice treated with XL184 (cabozantinib) (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days (You et al., 2011). Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg (Yakes et al., 2011). XL184 (cabozantinib) increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, XL184 (cabozantinib) disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 (cabozantinib) treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors ($P < 0.001$) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses ($P < 0.01$), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after whichtumors began growing at a rate similar to vehicle-treated control tumors. In addition, XL184 (cabozantinib) inhibited tumor growth ($P < 0.001$) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, $P < 0.0001$) when compared with pre dose tumor weights. Subchronic administration of XL184 (cabozantinib) was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang et al., 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 (cabozantinib) or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2019). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 (cabozantinib) treated animals appeared mostly normal. Thus, XL184 (cabozantinib) treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

2.2.2.1.2 Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED50) of targets was achieved at well

tolerated doses of XL184 (cabozantinib) and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2019). XL184 (cabozantinib) produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of XL184 (cabozantinib). This extended inhibition occurred in a manner that was generally predicted by plasma exposure, i.e., inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of XL184 (cabozantinib) resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2019). Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met (Yakes et al., 2011). This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

2.2.2.1.3 Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy (Investigator's Brochure, 2019). In rats, plasma concentrations in the range of 5 to 15 μM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations aslow as 0.1 μM were observed at highly efficacious doses in mice. These results were consistent with in vivo target modulation studies in mice which demonstrated long (4- to 10-hour) durationsof action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2019). In rats, the oral bioavailability of XL184 (cabozantinib) dosed as a solid was approximately 100% of XL184 (cabozantinib) dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [Cmax] and area under the time-concentration curve from 0 to t hours post-dose [AUC0-t] values) associated with single XL184 (cabozantinib) oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) (Investigator's Brochure, 2019). With repeat daily oral dosing in rats, systemic exposure (AUC0-t values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The Cmax and AUC0-t values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to XL184 (cabozantinib) in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (Cmax and AUC0-t values) associated with single XL184 (cabozantinib) oral doses in dogs increased less than dose-proportionally with increasing XL184 (cabozantinib) dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption (Investigator's Brochure, 2019). With repeat daily dosing, exposure (Cmax and AUC0-24 values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

2.2.2.1.4 Toxicology

In rodents and non-rodents, histopathological changes associated with XL184 (cabozantinib) administration were observed in GI tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues (Investigator's Brochure, 2019). Histopathological changes present in the bone and pancreas were considered secondary to XL184 (cabozantinib) administration. AEs following oral exposure to XL184 (cabozantinib) were generally dose- related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, XL184 (cabozantinib) administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen)when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg XL184 (cabozantinib) capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 (cabozantinib) was negative in an S. typhimurium/E.coli bacterial mutagenicity study, an in vitro chromosome aberration study using human peripheral blood lymphocytes, and an in vivo mouse bone marrow micronucleus study (Investigator's Brochure, 2019). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184 (cabozantinib)-treated rats or on cardiovascular function in XL184 (cabozantinib)-treated dogs.

2.2.2.2 Clinical Development of XL184 (Cabozantinib)

Patients have received XL184 (cabozantinib) in 18 Exelixis-sponsored clinical trials, 35 investigator-sponsored studies, and 19 NCI Cancer Therapy Evaluation Program (CTEP)-sponsored studies (XL184 [Cabozantinib] Investigator's Brochure, 2019). The 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, includingPK data, can be found in the XL184 (Cabozantinib) Investigator's Brochure (2019). Safety and efficacy information from the 2019 XL184 (Cabozantinib) Investigator's Brochure is summarized below.

2.2.2.3 Safety

Across Exelixis-sponsored studies with single-agent XL184 (cabozantinib), the most frequently observed 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, 2019). The most frequently observed 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.

2.2.2.4 Efficacy

The clinical activity of XL184 (cabozantinib) has been evaluated in pivotal trials in RCC, HCC, medullary thyroid cancer (MTC), and castrate-resistant prostate cancer (CRPC) (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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) (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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% 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 (stratifiedHR= 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 (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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 (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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) (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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 (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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 NSCLC,breast cancer, melanoma, ovarian cancer, glioblastoma (GB), and differentiated thyroid cancer (DTC).

2.2.2.5 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 (XL184 [Cabozantinib] Investigator's Brochure, 2019). 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.

2.3 Rationale

The clinical activity of PD-1/PD-L1 inhibitors (such as nivolumab) has been established in a wide range of tumor types. At the same time, the tolerability and efficacy of immunotherapy remains largely unknown in patients living with HIV on combination ART, who had generally been excluded from previous trials. In a recent systematic review of 13 studies involving 73 patients with HIV infection and advanced-stage cancers, immune checkpoint inhibitors (ICI, including nivolumab) were generally well-tolerated and were associated with anti-tumor activities (Cook et al. 2019). The ongoing phase 1 AMC-095 trial investigates ipilimumab and nivolumab in patients with HIV-associated malignancies, both solid tumors and Hodgkin Lymphoma (NCT02408861). As of March 1, 2019, the total enrollment for this study was 46 patients, including patients with KS, NSCLC, anal cancer, head and neck cancer, Hodgkin's lymphoma, and other malignancies. Among them, 36 were evaluated for response: 19 (53%) hadprogressive disease (PD) and 17 (47%) had stable disease (SD). Of the 21 enrolled patients who were in safety cohorts, 12 were evaluable for DLT and none of those have experienced a DLT. These preliminary results suggest the modest activity and general tolerability of this agent in patients with HIV infection. A recently published phase I study with pembrolizumab in patients with HIV and advanced cancer (n=30) also demonstrated modest clinical benefits (response rate of 10%) and tolerable safety (20% of grade 3 or higher pembrolizumab-related AEs) (Uldrick et al. 2019). Of note, one patient developed KS herpesvirus (KSHV)-associated B-cell lymphoproliferation and died.

PD-L1 expression by immunohistochemistry (IHC) on tumor cells and/or tumor-infiltrating immune cells, although imperfect, has been implicated as a predictive biomarker for PD-1/PD-L1 inhibitors in certain solid tumors. At the same time, as monotherapy, the clinical benefit of PD-1/PD-L1 inhibitors appears to be restricted to about 20% of unselected patients, many of them but not all with a high expression of PD-L1, thus suggesting that many tumors may use non-PD- 1/PD-L1 based mechanisms of immunotolerance (Borghaei et al., 2015, Garon et al., 2015, Doroshow et al., 2019, Reck et al., 2016). The PD-1/PD-L1 axis belongs to the CD28

family of receptors and the B7 family of ligands, which play key roles in the regulation of T-cellresponses by providing the co-stimulatory and co-inhibitory signals (Greenwald et al., 2005, Zang & Allison, 2007). HHLA2 (B7H7/B7H5/B7y), B7x (B7-H4/B7S1) and B7-H3 (CD276) are recently discovered new members of the immune checkpoint B7/CD28 family (Zang & Allison. 2007, Chinai et al., 2015, Zang et al., 2007, Zhao et al., 2013). As shown in figure 1, recent work (Cheng et al., 2018, Cheng et al., 2017 Janakiram et al., 2016) revealed that alternative immune checkpoints were widely expressed in lung cancer, breast cancer and other tumors. Intriguingly, the majority (78%) of PD-L1 negative lung cancers expressed these alternative immune checkpoints. Moreover, B7x-Ig and HHLA2-Ig inhibited T-cell receptor (TCR)-mediated proliferation of CD4 and CD8 T cells more robustly than PD-L1-Ig; all three significantly decreased cytokine production by T cells. These results implicate the potential roles of these alternative immune checkpoints in mediating immune escape mechanisms within the tumor microenvironment, apart from the PD-1/PD-L1 axis (Cheng et al., 2018, Cheng et al., 2017, Janakiram et al., 2016).

A.

Expression	B7-H3	B7x	HHLA2
Lung cancer	37-70%	31-69%	66-67%
Breast cancer	81-91%	95-98%	70%
Oral squamous cell carcinoma	75%	NA	NA
PD-L1 negative lung cancer	NA	69%	67%

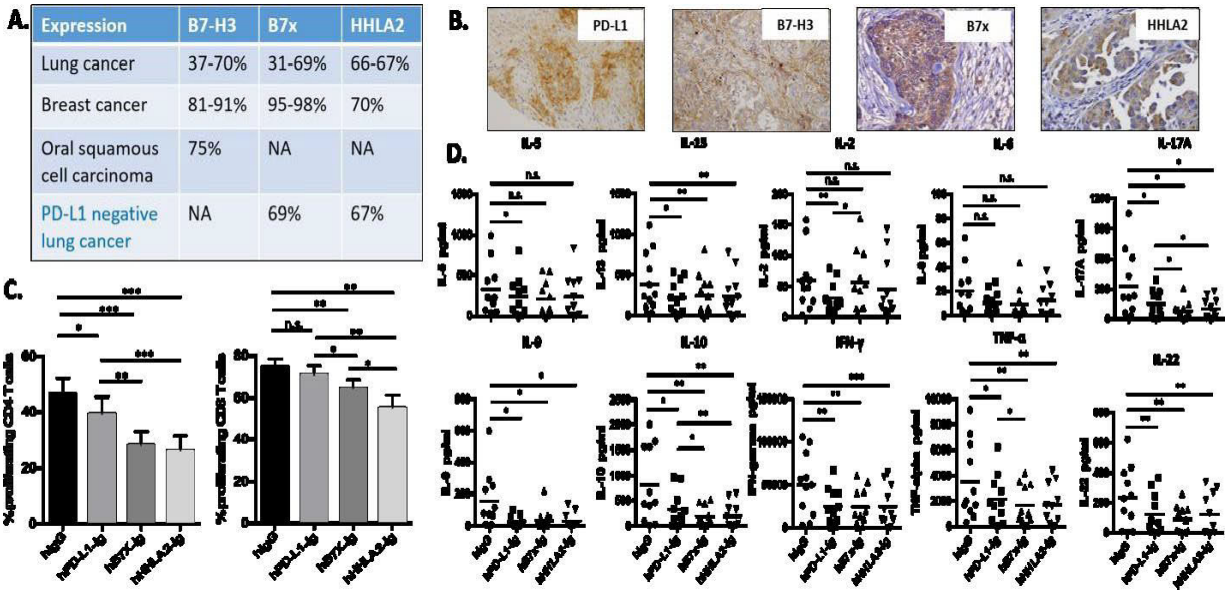


Figure 1: A. Expression of B7-H3, B7x and HHLA2 in selected tumor types. B. IHC: Representatives of PD-L1, B7-H3, B7x and HHLA2 expression in lung cancer. C. The inhibitory effects of PD-L1, B7x, and HHLA2 on TCR- mediated CD4 and CD8 T-cell proliferation (flow cytometry). D. Inhibition of PD-L1, B7x, and HHLA2 on cytokine production from T cells.

XL184 (cabozantinib) is an FDA-approved TKI for the treatment of MTC, RCC, and most recently for HCC, targeting VEGFR2, MET, ROS1, RET, KIT, and AXL. Its clinical activity

and tolerability have also been indicated in other types of malignancies, such as NSCLC (phase II ECOG-ACRIN 1512 trial) (Neal et al., 2016), urothelial, CRPC, and TNBC cancers. The AMC is conducting a phase 1 trial of XL184 (cabozantinib) in persons with HIV-associated solidtumors, including KS (AMC-087, NCT01822522). As of July 12, 2019, the total enrollment for the AMC- 087 study was 36 patients. The study will complete accrual by the end of the year. Among the enrolled patients to date, six (Stratum A with potent CYP-inhibiting ART, 60 mg dose level, 2 subjects; Stratum A, 40 mg dose level, 2 subjects; Stratum B with potent CYP-

inducing ART, 100 mg dose level, 2 subjects) have experienced a DLT, suggesting general tolerability of this agent in patients with HIV infection, particularly those taking non-CYP-inhibiting ART. There is, however, evidence of clinically evident drug-drug interactions with potent CYP-inhibiting ART, justifying reduced recommended doses of XL184 (cabozantinib). Five patients have remained on study therapy more than 2 years; three have remained on study therapy for more than 3 years, and one has remained on study therapy for over 5 years. Furthermore, evidence of antitumor activity has been observed in study patients with KS, follicular dendritic cell sarcoma, and head and neck squamous cell carcinoma. The encouragingearly clinical experience with this novel agent in HIV-infected patients with solid tumors and Kaposi sarcoma warrants additional investigation.

In addition to anti-angiogenic effects, XL184 (cabozantinib) is associated with an immune permissive tumor environment with immune-stimulatory activities. When combined with CEA-specific tumor vaccine in murine models, XL184 (cabozantinib) significantly reduced tumor growth and led to durable tumor regression (Kwilas et al., 2014, Kwilas et al., 2015). It increased the expression of tumor cell markers associated with immune recognition and CEA- specific tumor lysis by T cells. XL184 (cabozantinib) was also reported to clear murine prostatecancer via activating neutrophil mediated antitumor innate immunity (Patnaik et al., 2017).

Furthermore, XL184 (cabozantinib) modified the immune microenvironment, through potentiating the function and infiltration of cytotoxic T cell, as well as regulating the number of immunosuppressive cells [such as T regulatory (Treg), myeloid-derived suppressor cells (MDSC,) and tumor-associated macrophages] (Kwilas et al., 2014, Kwilas et al., 2015).

Interestingly, in a mouse model of prostate cancer, even monotherapy exerted minimal anti-tumor effects, the combination of immunotherapy and XL184 (cabozantinib) demonstrated powerful synergistic response, likely through promoting IL-1 receptor antagonists and ablation of MDSC-related cytokines (Lu et al., 2017). Moreover, XL184 (cabozantinib) treatment has been reported to significantly decrease Tregs in patients with advanced/refractory metastatic urothelial carcinoma (Apolo et al., 2014). Observations from other recent clinical studies also implicate that the combination of XL184 (cabozantinib) with nivolumab may modify the tumor microenvironment, re-sensitize the tumors to ICIs, and thereby reverse the resistance to immunotherapy (Leal et al., 2017, Nadal et al., 2018).

There are ongoing trials testing the combination of nivolumab and XL184 (cabozantinib) in a variety of solid tumors, such as breast cancer (NCT03316586), HCC (NCT03299946, NCT01658878), endometrial cancer (NCT03367741), NSCLC (EA5191), renal (CheckMate9ER, NCT03141177), and genitourinary (GU) cancers (NCT02496208). In these studies, XL184 (cabozantinib) at 40 mg daily and nivolumab at 480 mg every 4 weeks are frequently recommended. In the GU studies, the combination of nivolumab/XL184 (cabozantinib) was reported to have manageable toxicity (no DLTs) and durable clinical activity

(Nadal et al., 2018, Nadal et al., 2017). More intriguingly, in two recently published phase 3 trials in metastatic RCC (KEYNOTE-426 and JAVELIN Renal 101), the combination of PD-1/PD-L1 inhibitor and VEGFR inhibitor therapy (regimens similar to nivolumab/ XL184 [cabozantinib]) was associated with significantly longer survivals and higher response rates compared to standard- of-care sunitinib (Motzer et al., 2019, Rini et al., 2019). It is expected

thatthese combinations will become new standards of care in managing patients with metastatic RCC. On the other hand, these studies either excluded HIV patients on ART or were not specifically designed to test such combinations in HIV patients on ART.

The next logical step is to investigate the combined treatment of nivolumab and XL184 (cabozantinib) in HIV patients with advanced solid tumors. The specific need for a separate study in HIV patients is as follows: 1) There are potential drug-drug interactions, especially between XL184 (cabozantinib) and CYP-inhibiting ART. XL184 (cabozantinib) is a substrate ofCYP 3A4. A number of ARTs are associated with CYP 3A4 inhibition or induction, which may cause significant drug-drug interactions thereby impairing efficacy or increasing toxicity. In the AMC- 087 study, significant drug-drug interactions with potent CYP-inhibiting ARTs (either ritonavir or cobicistat-boosted regimens) necessitated dose modification of XL184 (cabozantinib). 2) Relatively few patients with HIV infection are enrolled in CTEP-sponsored trials performed within the NCTN, and HIV infection remains an exclusion criterion in the majority of pharmaceutical- sponsored trials. 3) There is lack of data investigating the effects of immunotherapy or XL184 (cabozantinib) on the latent HIV viral reservoir. The latent HIV reservoir is a major hurdle to cure HIV infection. Reactivation of this reservoir may lead to rebound viremia (Vanhamel et al., 2019). The central memory CD4 T cells have been implicated as the key reservoir (Vanhamel et al., 2019). Evidence suggests a significant enrichment of HIV latency in PD-1 high CD4 memory T cells; and PD-1 signaling may play important roles in the initiation and continuation of HIV latency (Fromentin et al., 2019, Evans et al., 2018). At the same time, there are inconsistent reports on the influence of anti-PD-1 inhibitors on HIV latency in cancer patients (Fromentin et al., 2019, Scully et al., 2018, Guihot et al., 2018). It also remains unknown how XL184 (cabozantinib) may impact the HIV reservoir. 4) As aforementioned, the preliminary results of the AMC-095 study and the phase 1 pembrolizumab (Uldrick et al., 2019) study revealed modest responses of checkpoint inhibition so far in HIV patients with advanced cancers. Interestingly, preliminary data on the HIV/lung cancer cohort at Albert Einstein showed remarkably low expression of PD-L1 in this patient population. These observations might explain the somewhat low activity with single- agent immunotherapy and further justify the need for novel combinations to improve therapeutic efficacy. 5) KS remains as one of the most common AIDS-defining malignancy in the USA even in the ART era (Biggar et al., 2007). As a single agent, both nivolumab and XL184 (cabozantinib) are generally tolerated and have clinical activity in patients with HIV-associated KS: the preliminary analysis of the AMC-095 trial revealed 75% (9) of SD to nivolumab, while a retrospective study showed RR of 63% (n=9, including 8 received nivolumab and 1 received pembrolizumab) (Cook et al., 2019; Galanina et al., 2018). On the other hand, both VEGF/VEGFR and MET signaling (targets of XL184 [cabozantinib]) have been implicated in the pathogenesis of KS (Maier et al., 1996; Masood et al., 1997). As shown in the AMC-087 trial, XL184 (cabozantinib) was associated with a 31% RR in KS. Moreover, in a phase 2 study including mostly pretreated patients with HIV-associated KS, Bevacizumab (another anti-VEGF agent), also demonstrated clinical activity (RR=31%, SD=56%) (Uldrick et al., 2012).

Furthermore, there is lack of data and trial to investigate the combination regimen of XL184 (cabozantinib)/nivolumab in KS patients. This study is the first feasibility study in this particular patient population. 6) This study is complimentary to the EA5191 study in NSCLC and builds on both AMC-087 and AMC-095 studies. Both AMC trials are anticipated to complete accrual soon, such as later this year for the AMC-087 study. 7) Previous studies suggest that XL184

(cabozantinib) might modify the immune microenvironment and sensitize tumors to immunotherapy (Kwilas et al., 2014; Kwilas et al., 2015; Lu et al., 2017; Leal et al., 2017; Nadal et al., 2018; McDermott et al., 2018). We hypothesize that XL184 (cabozantinib) might prime tumors to PD-1/PD-L1 inhibitors. Thus, for potentially better priming effects, this trial has a two-week period for XL184 (cabozantinib) alone followed by the combined treatment.

2.4 Correlative Studies Background Integrated Studies

2.4.1 PD-L1 expression

PD-L1, as a key immune checkpoint, play crucial roles in mediating immune escape mechanisms. The expression of PD-L1 has been implicated as a potential predictive biomarker for PD-1/PD-L1 inhibitors in certain solid tumors. PD-L1 expression may predict treatment efficacy. Pembrolizumab, a PD-1 inhibitor, has been investigated as monotherapy (Reck et al., 2016). It was initially approved in the second line setting for patients with advanced NSCLC with PD-L1 TPS ≥1%, subsequently was granted approval as the first-line treatment for PD-L1 TPS ≥50% , with expansion to PD-L1 TPS ≥1% (Herbst et al., 2016; Mok et al., 2019). A number of studies also suggest that PD-L1 expression, although imperfect, may also be associated with clinical efficacy of other PD-1/PD-L1 inhibitors, such as nivolumab.

2.4.2 CD4, CD8 counts, and HIV Viral Load

Nivolumab and XL184 (cabozantinib) may affect CD4, CD8 counts, and HIV viral load. As patients with HIV have typically been excluded from large pharmaceutical studies, effects of immune checkpoint inhibition and XL184 (cabozantinib) on CD4 and CD8 counts or HIV viral load are not well described.

2.4.3 Exploratory

2.4.3.1 Tumor microenvironment analysis through the multiplex quantitative immunofluorescence (MQIF) assay

Evidence suggests that XL184 (cabozantinib) may modify the tumor immune microenvironment by its angiogenetic effects, as well as potentiating both the function and infiltration of cytotoxic T cells, in addition to regulating the quantity of immunosuppressive cells. The change of key components in tumor microenvironment may correlate with XL184 (cabozantinib) treatment efficacy. XL184 (cabozantinib) alone decreased Tregs in advanced or refractory metastatic urothelial carcinoma (Apolo et al., 2014); findings from another suggested that XL184 (cabozantinib) with nivolumab can modify the tumor microenvironment and induce immune checkpoint inhibitor sensitivity in tumors (Leal et al., 2017; Nadal et al., 2018).

2.4.3.2 Latent HIV Reservoir

Memory CD4+ T cells have been implicated as the key latent HIV reservoir, reactivation of which may lead to rebound viremia (Vanhamel et al., 2019). PD-1-high memory CD4+ T cells may have more HIV latency; furthermore, PD-1 signaling may play a part in the initiation and continuation of HIV latency (Fromentin et al., 2019; Evans et al., 2018). Nivolumab and

XL184(cabozantinib) may affect the latent HIV reservoir. There are inconsistent reports on the influence of immune checkpoint inhibition on the latent HIV reservoir among cancer patients (Fromentin et al., 2019; Scully et al., 2018; Guihot et al., 2018). The effect of XL184 (cabozatinib) on the HIV reservoir is also unknown.

2.4.3.3 Immune cell subsets and activation

Changes in the tumor microenvironment can affect efficacy of immune checkpoint inhibition. XL184 (cabozantinib), on the other hand, may modify the tumor microenvironment. XL184 (cabozantinib) will increase the quantity of cytotoxic T cells and regulate immunosuppressive cells. XL184 (cabozantinib) has been shown to potentiate the function and infiltration of cytotoxic T cells and also regulate the quantities of immunosuppressive cells, including regulatory T cells, MDSCs, and tumor-associated macrophages (Kwilas et al., 2014; Kwilas et al., 2015).

2.4.3.4 Cytokine

Cytotoxic T cells produce cytokines that play a role in tumor lysis. Immune checkpoint inhibition will increase T cell production of cytokines. PD-L1, and alternative immune checkpoints such as B7x and HHLA2 inhibited T-cell receptor-mediated CD4 and CD8 T cellproliferation and decreased cytokine production (Cheng et al., 2018; Cheng et al., 2017; Janakiram et al., 2016).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥18 years. Children are excluded from this study, but will be eligible for future pediatric trials.

3.1.2 For the six-patient safety cohort, subjects must have histologically or cytologically confirmed advanced solid tumors that are metastatic or recurrent, and require palliative systemic treatment, for which there are either FDA approved indications for XL184 (cabozantinib) or nivolumab or have at least phase 2 data clearly indicating activity (such as RCC, HCC, MTC, melanoma, NSCLC, Head and neck cancer, Urothelial Carcinoma, SCLC, radioiodine-refractory differentiated thyroid cancer, ovarian cancer, CRPC, and TNBC). Subjects must have progressed, or are intolerant, or decline systemic therapy associated with clinically significant survival benefit if checkpoint blockade is not an approved or accepted treatment.

The expansion cohort is limited to subjects with KS. Histologic, cytologic, and pathologic confirmation of KS is required.

3.1.3 Any number of prior cancer therapies will be permitted, including treatment naïve subjects. (Note: For KS, treatment naïve asymptomatic subjects will be permitted. But treatment naïve KS subjects with visceral symptomatic disease or complicated KS HHV 8 disease including Castleman’s disease will be excluded and should receive front-line

standard of care).

3.1.4 ECOG performance status of 0-1 (Karnofsky ≥80%, see Appendix A).

3.1.5 Subjects with tumors other than KS must have evaluable disease.

3.1.6 Subjects must have adequate organ and marrow function as defined below:

– absolute neutrophil count	≥1,000/mcL
– platelets	≥75,000/mcL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (If, however, the participant has Gilbert's disease or unconjugated hyperbilirubinemia that is considered to be secondary to antiretroviral therapy, then the total bilirubin must be ≤3 × ULN)
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional ULN
– creatinine	≤1.5 institutional ULN OR
– creatinine clearance (CrCl)	≥50 mL/min (if using the Cockcroft-Gault formula below):

Female CrCl = (140 - age in years) × weight in kg × 0.85 72 × serum creatinine in mg/dL

Male CrCl = (140 - age in years) × weight in kg × 1.00 72 × serum creatinine in mg/dL

– hemoglobin	≥9 g/dL
– CD4 count	≥50/mcL

3.1.7 Subjects must have known HIV infection as below: Serologic documentation of HIV infection at any time prior to study entry, as evidenced by positive ELISA, positive Western blot, or any other federally approved licensed HIV test. Alternatively, this documentation may include a record that another physician has documented that the participant has HIV infection based on prior ELISA and Western blot, or other approved diagnostic tests.

Subjects must receive appropriate care and treatment for HIV infection. An eligible patient should be on ART that is not strongly CYP3A4 inhibiting or otherwise prohibitedby the protocol (e.g. drug-drug interactions) or the patient must be converted to one of these regimens before starting investigational therapy in order to avoid dose modulation of cabozantinib

3.1.8 Life expectancy of ≥12 weeks.

3.1.9 For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.10 Subjects with a history of hepatitis C virus (HCV) infection must have been treated and cured including self-cured cases. For subjects with HCV infection who are currently on

treatment, they are eligible if they have an undetectable HCV viral load.

3.1.11 Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.12 The effects of nivolumab and XL184 (cabozantinib) 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 investigational drug. WOCBP must have a negative serum or urine pregnancy test within 72 hours prior to the start of receiving the first dose of the study medication. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab 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 investigational product. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception.

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

3.1.13 Ability to understand and the willingness to sign a written informed consent document. Subjects with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 For the safety run-in cohort, subjects who have received prior XL184 (cabozantinib), PD-1/PD-L1 inhibitor, or VEGFR inhibitor are ineligible. Prior treatment with these agents is allowed for the expansion KS cohort.

3.2.2 Subjects on potent CYP3A4-inhibiting agents are ineligible, such as:

- Antiretroviral: ritonavir, cobicistat, indinavir, atazanavir, delaviridine
- Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole, posaconazole
- Antidepressants: nefazodone
- Antidiuretic: conivaptan
- GI: cimetidine, aprepitant
- Hepatitis C: boceprevir, telaprevir
- Miscellaneous: Seville oranges, grapefruit, or grapefruit juice and/or pummelos, star fruit,exotic citrus fruits, or grapefruit hybrids

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference such as https://www.drugbank.ca/categories/DBCAT002647 or https://www.crediblemeds.com. The latter requires free registration to check QTDrugs List. As part of the enrollment/informed consent procedures, the subject 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 subject is considering a new over-the-counter medicine or herbal product.

Of note, to meet the eligibility requirement, subjects are allowed to convert their antiretroviral medications to one of the regimens not including potent CYP3A4-inhibiting agents, when the subjects have progressed, are intolerant, or decline the standard systemic therapy for their advanced tumors.

Subjects must receive appropriate care and treatment for HIV infection, including antiretroviral medications, when clinically indicated (including no ART) and should be underthe care of a physician experienced in HIV management. Subjects will be eligible provided there is no intention to initiate therapy or the regimen has been stable for at least 4 weeks with no intention to change the regimen within 8 weeks following study entry.

To enroll in the study, the participants should be on the protocol accepted ART as long as they are receiving XL184 (cabozantinib)

3.2.3 Subjects who have had cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies) within 3 weeks, or nitrosoureas/mitocycin C within 6 weeks before the first dose of study treatment, or those who have not recovered from AEs due to agents administered more than 4 weeks earlier.

3.2.4 The subject has received radiation therapy:

- to the thoracic cavity, abdomen, or pelvis within 4 weeks before the first dose of study treatment, or has ongoing complications, or is without complete recovery and healing from prior radiation therapy
- to bone or brain metastases within 14 days before the first dose of study treatment
- to any other site(s) within 21 days before the first dose of study treatment.

3.2.5 Subjects who are receiving any other investigational agents.

3.2.6 Subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to enrollment. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab or XL184 (cabozantinib).

3.2.8 The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 7 days before the first

dose of study treatment.

3.2.9 The subject has a primary brain tumor, active brain metastases or epidural disease. Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or participants with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible. Subjects with treated brain metastasis should not take enzyme-inducing anticonvulsive therapies (EIACDs) within 2 weeks of registration, though non-enzyme inducing anticonvulsive drugs such as levetiracetam are allowed. Neurosurgical resection of brain metastases or brain biopsy is permitted if completed at least 3 months before starting study treatment. Baseline brain imaging with contrast-enhanced CT or MRI scans for participants with known brain metastases is required to confirm eligibility. Subjects with untreated CNS metastases are eligible if they are not symptomatic and the lesions are less than 1 cm in size. CNS metastases should be stable for at least 4 weeks, neurologically asymptomatic and without corticosteroid treatment at time of first dose of study treatment.

3.2.10 Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:
- Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
- Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

3.2.11 The subject has experienced any of the following:

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

3.2.12 The subject has radiographic evidence of cavitating pulmonary lesion(s).

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

3.2.14 The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor

within 28 days before the first treatment.

3.2.15 The subject has uncontrolled and significant cardiovascular disorders:

- Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening.

- Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment.

- The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before treatment.

  Note: if initial QTcF is found to be >500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤500 ms, the subject meets eligibility in this regard.

- Any of the following within 6 months before the first dose of study treatment:
  - Unstable angina pectoris
  - Clinically-significant cardiac arrhythmias
  - Stroke
  - Myocardial infarction
  - Subjects with a venous filter (e.g. vena cava filter) are not eligible
  - thromboembolic event

3.2.16 The subject has uncontrolled and significant disorders particularly those associated with a high risk of perforation or fistula formation including:

Any of the following within 28 days before the first dose of study treatment:
- Active and symptomatic peptic ulcer disease
- Evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation should be evaluated for the potential need for additional treatment before coming on study.

Any of following within 6 months before the first dose of study treatment:
- Abdominal fistula
- Gastrointestinal perforation
- Bowel obstruction or gastric outlet obstruction Intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before

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

3.2.17 Subjects with active autoimmune disease or history of autoimmune disease that might

recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to subjects with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and subjects 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. Subjects with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids areeligible. Subjects with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and subjects with positive serology, suchas antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.18 Major surgery (e.g., laparoscopic nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 2 weeks before first dose of study treatment. Minor surgeries within 10 days before first dose of study treatment. Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

3.2.19 The subject is unable to swallow tablets.

3.2.20 History of organ transplant or stem cell transplant.

3.2.21 Subjects with uncontrolled intercurrent illness.

3.2.22 Subjects with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.23 Pregnant women are excluded from this study because XL184 (cabozantinib) has the potential for teratogenic or abortifacient effects, and the effects of nivolumab 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) or nivolumab.

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 subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account 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) 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 such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- 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 acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

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 SSW for Local Context 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 email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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

- Holds an active CTEP status,
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster,

- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site 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 (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration 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 to institutions and its associated investigators and staff or on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of the 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 PA015, and protocol number 10387
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For *10387* Site Registration

- 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 using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the *Regulatory* section, and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

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 LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS 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: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the 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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may 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 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 Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *[# of days]* 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

Time Point	Specimen	Send Specimens To:
Archival		
	• 1 Formalin-fixed paraffin-embedded (FFPE) tumor tissue block preferred[1,2] *If a block is not available, then submit:* • 10 – 20 (5 µm) slides FFPE tumor tissue (a minimum 5) [2]	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center
Baseline		
	• 1 × 5 mL lavender top tube peripheral blood (mandatory) • 1 × 5 mL pearl top tube peripheral blood	Local Testing

	(mandatory)	
	• 4 × 8.5 mL red top tubes peripheral blood[2] • 3 × 8.5 mL yellow top tubes peripheral blood [2]	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center
Cycle 1 Day 1 (after the 14-day XL184 (cabozantinib) lead-in)		
	• 1 × 5 mL lavender top tube peripheral blood (mandatory) • 1 × 5 mL pearl top tube peripheral blood (mandatory)	Local Testing
Cycle 3 Day 1		
Prior to study treatment administration	• 1 × 5 mL lavender top tube peripheral blood (mandatory) • 1 × 5 mL pearl top tube peripheral blood (mandatory)	Local Testing
	• 4 × 8.5 mL red top tubes peripheral blood[2] • 3 × 8.5 mL yellow top tubes peripheral blood [2]	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center
Cycle 5 Day 1		
Prior to study treatment administration	• 1 × 5 mL lavender top tube peripheral blood (mandatory) • 1 × 5 mL pearl top tube peripheral blood (mandatory)	Local Testing
	• 4 × 8.5 mL red top tubes peripheral blood[2] • 3 × 8.5 mL yellow top tubes peripheral blood [2]	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center
During Treatment – Every 12 Weeks (e.g. Day 1 of Cycle 8, 11, etc.)		
	• 1 × 5 mL lavender top tube peripheral blood (mandatory) • 1 × 5 mL pearl top tube peripheral blood (mandatory)	Local Testing
Treatment discontinuation		
	• 4 × 8.5 mL red top tubes peripheral blood[2] • 3 × 8.5 mL yellow top tubes peripheral blood [2]	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center

[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 – 20).

[2] The research specimens are optional.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Scheduling of Specimen Collections

See Table 5.1 for the study collection timepoints of correlative samples. Please adhere to the following guidelines below when scheduling procedures to collect blood:

- Specimens submitted frozen can be collected Monday through Friday but must be stored frozen and shipped to the **Local Testing Lab/ Cheng Laboratory** on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -80°C freezer.
- Fresh blood specimens must be collected and shipped Monday through Thursday to ensure delivery by Friday.

5.3 Specimen Tracking System Instructions

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 3.
- Additional Requirements:
    - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other 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 analysisof 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, date of birth, 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.

The Shipping List report **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 (Time to be added by hand)

5.3.2.2 Tissue Specimen Labels

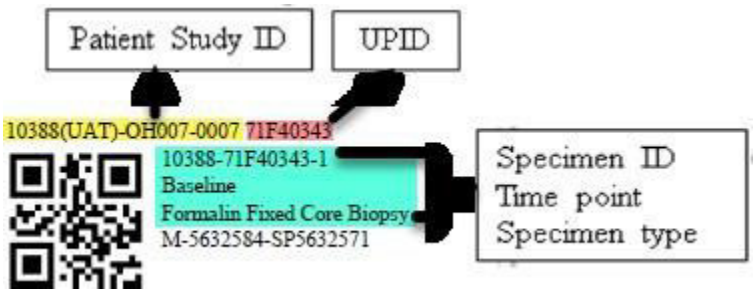
Include the following on all tissue specimens or containers (e.g., formalin jar):

- 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, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.3.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimensfolder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



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

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following 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. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time.
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 PatientID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the finalregistration step.

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

5.3.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

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 the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label. After collection, store labeled specimens as described in Section 5.5. (5.3.2)
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Bone Marrow, Molecular Reports (up to 4), and Surgical (or Operative) reports. 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) and/or the Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted**. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand writing).

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 sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

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

- Shipping List report is available at the site level.
- 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).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.4 Specimen Collection

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

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

- Tissue must have been collected within 12 months prior to registration, optimally within 6 months or even closer prior to registration
- 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 mm2 is optimal. Minimum is 5 mm2.
    - Volume: 1 mm3 optimal. Minimum volume is 0.2 mm3, however the success of DNA extraction decreases at suboptimal tissue volume.

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

- A minimum of 5 (optimally 10-20) unstained sections, 5 µm, on positively charged slides

Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n).

See Section 5.3.2 for labeling instructions.

5.4.2 Blood Collection

5.4.2.1 Collection of Blood in Red Top Tube for Serum Processing

1. Label four 8.5 mL red-top tube according to the instructions in Section 5.3.2.
2. Collect approximately 8 mL of whole blood in each red-top tube.
3. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours. Process serum from red top tubes by centrifuging for 10 minutes at 1,200 × g at room temperature.
4. **Using a clean transfer pipette**, aliquot serum into the labeled (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.3.2) cryovials at an aliquot volume of 1 mL per tube. Avoid picking up red blood cells

when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of serum specimens should be completed within 1 hour of centrifugation.

5. Store serum cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.

5.4.2.2 Collection of Blood in Yellow Top (acid citrate dextrose, ACD) Tubes for Whole Blood Processing (Specimen purpose: "HIV latent reservoir")

1. Label three 8.5ml ACD tubes according to the instructions in Section 5.3.2.
2. Collect approximately 8mL blood in each ACD tube and gently invert tubes to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.5.
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.4.2.3 Specimen Collection for Local Laboratories

Blood for the CD4, CD8 counts, and HIV Viral Load studies should be collected in lavender top tubes (1 x 5mL) and pearl top tubes (1 x 5 mL) at baseline, Day 1 of Cycle 1 (after the 14 day XL184 (cabozantinib) lead-in, Day 1 of Cycle 3 (prior to administering study treatment), Day 1 of Cycle 5 (prior to administering study treatment), every 12 weeks, and treatment discontinuation. The blood should be handled and/or shipped following institutional SOPs as perstandard of care.

5.5 Shipping of Specimens from Clinical Site to Other Laboratories

5.5.1 Shipping of Specimens to Cheng Laboratory

Shipping of Specimens to Cheng Laboratory (including tumor biopsies and blood specimen forlatent HIV Reservoir studies)

5.5.1.1 Specimen Shipping Instructions:

5.5.1.1.1 Archival Tissue:

BLOCK (preferred): Submit only ONE block per accession; Label the block with the local laboratory block/surgical ID; SLIDES: The slides should be cut freshly from one single block; Aminimum of 5 unstained (optimally 10-20) sections, 5 µm, should be cut and lifted onto positively charged slides; Place the slides into the slot slide.

*Send corresponding pathology report for each FFPE specimen. Ensure dry ice is available in advance for shipment

5.5.1.1.2 Blood

To ship blood, place tubes into a container [such as canister of a STP-100 SAF-T-PAK shipper

(VWR# 11217-163)] wrapping each tube in bubble wrap and using the absorbent paper at the bottom of the container. Specimens MUST BE SHIPPED Monday through Thursday as an OVERNIGHT PRIORITY shipment. Aliquots should be frozen at -80 C and shipped on dry ice.

5.5.1.2 Shipping Address:

Haiying Cheng
Albert Einstein Cancer Center
Chanin 407, 1300 Morris Park Avenue
Bronx, NY 10461

PH: 718 -430-2000, ext 6443
Email: hcheng@montefiore.org

5.5.1.3 Contact Information for Assistance:

Haiying Cheng
Phone: 718-430-2000, ext 6443
E-mail: hcheng@montefiore.org

5.6 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay and CLIA: Y/N	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory, Lab PI, and Lab PI Email
Tissue-based							
1	PD-L1 expression	IHC (monoclonal mouse anti-PD-L1, clone 22C3) CLIA: N	Integrated To investigate whether pre-treatment PD-L1 expression may predict treatment efficacy	FFPE Tumor tissue	Archival	O	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center Haiying Cheng, MD, PhD
2	Tumor microenvironment analysis through the multiplex quantitative immunofluorescence (MQIF) assay	MQIF CLIA: N	Exploratory To investigate whether the pretreatment expression of immune checkpoints, infiltrating immune cell and angiogenesis markers may predict treatment efficacy and resistance.	FFPE Tumor tissue	Archival	O	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center Haiying Cheng, MD, PhD
Blood-based							

Priority	Biomarker Name	Assay and CLIA: Y/N	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory, Lab PI, and Lab PI Email
1	CD4, CD8 counts, and HIV Viral Load	Standard of Care Evaluation CLIA: Y	Integrated To describe and monitor the impact of XL184 (cabozantinib) and nivolumab combination on ART therapy	Peripheral blood	Baseline, Day 1 of Cycle 1 (after 14 day XL184 (cabozantinib) lead-in), Day 1 of Cycle 3 (prior to treatment administration), Day 1 of Cycle 5 (prior to treatment administration), then every 12 weeks, and at treatment discontinuation	M	Local Testing
2	Latent HIV Reservoir	Latent HIV Reservoir testing CLIA: N	Exploratory To determine the effects of nivolumab and XL184 (cabozantinib) on HIV Reservoir	Peripheral blood	Baseline, Day 1 of Cycle 3 (prior to treatment administration), Day 1 of Cycle 5 (prior to treatment administration), and at treatment discontinuation	O	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center Haiying Cheng, MD, PhD Note: The PI will collect the whole batch and later send them to Accelevir Diagnostics, LLC

Priority	Biomarker Name	Assay and CLIA: Y/N	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory, Lab PI, and Lab PI Email
3	Immune cell subsets and activation	Assay to check immune cell subsets and activation CLIA: N	Exploratory To determine the effects of nivolumab and XL184 (cabozantinib) on immune cell subsets and activation	Peripheral blood	Baseline, Day 1 of Cycle 3 (prior to treatment administration), Day 1 of Cycle 5 (prior to treatment administration), and at treatment discontinuation	O	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center Haiying Cheng, MD, PhD
4	Cytokine	Human multiplex Cytokine Assay CLIA: N	Exploratory To determine the effects of nivolumab and XL184 (cabozantinib) cytokine production	Peripheral blood	Baseline, Day 1 of Cycle 3 (prior to treatment administration), Day 1 of Cycle 5 (prior to treatment administration), and at treatment discontinuation	O	Cheng Laboratory, Montefiore Medical Center, Albert Einstein Cancer Center Haiying Cheng, MD, PhD

5.7 Integrated Correlative Studies

5.7.1 PD-L1 Expression

5.7.1.1 Specimen(s) Receipt and Processing at the Pathology Laboratory at the Montefiore Medical Center

We will assess baseline expression level of PD-L1 expression in archival FFPE tumor tissue using IHC. Sections cut from FFPE blocks will be deparaffinized and subjected to heat induced epitope retrieval. Slides will be incubated with primary antibody (monoclonal mouse anti-PD-L1, clone 22C3) and visualized using EnVision FLEX system on Dako Autostainer Link 48. Protein expression will be determined by using tumor proportion score which is percentage of tumor cells showing PD-L1 membrane staining. PD-L1 stained tissue samples will be scored as PD-L1 positive if membrane staining is observed in more than 1% of tumor cells among a minimum of 100 evaluable tumor cells.

5.7.1.2 Site Performing Correlative Study

PD-L1 expression analysis will be conducted at the Albert Einstein Cancer Center under the leadership of Drs. Haiying Cheng and Xingxing Zang.

5.7.1.3 Contact information for notification of specimen shipment.

Refer to Section 5.5.

5.7.2 CD4, CD8 counts, and HIV Viral Load

5.7.2.1 Specimen Receipt and Processing at Local Testing Laboratories as per standard of care at each distinct institution.

5.7.2.2 Site Performing Correlative Study
This assay will be performed at the local lab of each distinct institution as per their standard of care.

5.7.2.3 Contact information for notification of specimen shipment Refer to Section 5.5.

5.8 Exploratory/Ancillary Correlative Studies

5.8.1 Tumor microenvironment analysis through the multiplex quantitative immunofluorescence (MQIF) assay (Archival tissue only)

5.8.1.1 Specimen Receipt and Processing at the Pathology Laboratory at the Montefiore Medical Center

Baseline expression of PD-L1 and alternative immune checkpoints will be assessed. Sections cut from FFPE blocks will be deparaffinized and subjected to heat induced epitope retrieval.

5.8.1.2 Site(s) Performing Correlative Study

Tumor microenvironment analysis by MQIF will be conducted at the Albert Einstein Cancer Center under the leadership of Drs. Haiying Cheng and Xingxing Zang.

5.8.1.3 Contact information for notification of specimen shipment Refer to Section 5.5.

5.8.2 Latent HIV Reservoir

5.8.2.1 Specimen(s) Receipt and Processing at Accelevir Diagnostics LLC

Blood collected from study subjects into three 8.5-mL yellow top tubes will be rotated gently 2-3 times, then centrifuged. Plasma will be removed in 0.5mL aliquots and placed into 1.5-mL NUNC tubes to be transferred to liquid nitrogen storage. Depending on volume, remaining cells and plasma will be transferred into a 15-mL conical tube or 50-mL centrifuge tube, to which sterile PBS will be added in equal volume and pipetted to mix. The mixture will be overlaid on to 4-5mL room-temperature LSM or Ficoll-Hypaque solution in a sterile 15-mL conical centrifuge tube. When centrifuged, the mononuclear leukocytes will band at the interface of plasma and LSM as a fluffy white layer and should be aspirated off for transfer to a labeled 15-mL sterile conical centrifuge tube, with the minimum amount of LSM or Ficoll-Hypaque. Three volumes of PBS, or enough to fill the conical tube, will be added to the cell suspension and mixed by pipetting. After centrifugation, supernatant will be aspirated off, and the pellet will be resuspended in 12 mL PBS, and centrifuged again to wash the cells. The DMSO freezing mixture will be added dropwise to resuspend the cells, using a 1-mL pipette; this will be frozen in 0.5-mL aliquots in sterile NUNC vials, then transferred to the liquid nitrogen freezer for long-term storage.

5.8.2.2 Site(s) Performing Correlative Study

Latent HIV reservoir analysis will be conducted at Accelevir Diagnostics, LLC.

5.8.2.3 Contact information for notification of specimen shipment Refer to Section 5.5.

5.8.3 Immune cell subsets and activation

5.8.3.1 Specimen Receipt and Processing at the Pathology Laboratory at the Montefiore Medical Center

Blood collected from study subjects into two 8.5-mL red top tubes will be centrifuged to isolate peripheral blood mononuclear cells (PBMC), and flow cytometry will be performed to quantify populations of CD4 T cells, CD8 T cells, Tregs, myeloid-derived suppressor cells (MDSC), B cells, neutrophils, NK cells, and macrophages; CD4, CD8, and Tregs will be tested for markers of activation.

5.8.3.2 Site Performing Correlative Study

Immune cell subset and activation analysis will be conducted at the Albert Einstein Cancer Center under the leadership of Drs. Haiying Cheng and Xingxing Zang.

5.8.3.3 Contact information for notification of specimen shipment Refer to Section 5.5.

5.8.4 Cytokine

5.8.4.1 Specimen Receipt and Processing at the Pathology Laboratory at the Montefiore Medical Center

Blood collected from study subjects into two 8.5-mL red top tubes will be evaluated using the human multiplex cytokine assay.

5.8.4.2 Site Performing Correlative Study

Cytokine analysis will be conducted at the Albert Einstein Cancer Center under the leadership of Drs. Haiying Cheng and Xingxing Zang.

5.8.4.3 Contact information for notification of specimen shipment

Refer to Section 5.5.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. 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	**Premedication; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
XL184 (Cabozantinib)	Per physician discretion Take on an empty stomach, do not eat at least 2 hours before and 1 hour after each	40 mg	PO	Daily14 days before Cycle 1 starts. Daily on days 1-28 in ≥ Cycle 1, for	28 days (4 weeks)

	dosing.				
Nivolumab	Per physician discretion	480 mg	IV See Section 6.1.1 for administration details	Day 1 each cycle.	
PO = Oral; IV = Intravenous Treatment will be continued until criteria for removal from the study are met (See Section 6.5 Duration of Therapy)					

Subjects in the safety run-in will receive 40 mg XL184 (cabozantinib) by mouth (PO) once daily, for 2 weeks. After two weeks, the subject is treated with nivolumab at 480 mg every 4 weeks while continuing the daily 40 mg XL184 (cabozantinib).

The safety run-in part of the study will be a modified 3 + 3 design. Up to 3 subjects will be treated in the first cohort. If ≤1/3 subjects experience DLT, the dose level cohort will be expanded to 6 subjects. If ≤1/6 subjects experience DLT, the dose will be considered as the dosefor the expansion cohort. If ≥2 subjects experience DLT, this regimen will be considered unworthy for further development and the study will be closed.

At the expansion cohort, 12 additional subjects with KS would be enrolled to gather more data on safety and correlative studies.

In the absence of treatment delays due to adverse event(s), treatment with nivolumab and XL184 (cabozantinib) may continue for up to 1 year, or 1 year after a partial response is achieved, or 6 months after a complete response is achieved until one of the following criteria applies: disease progression, intercurrent illness that prevents further administration of treatment, pregnancy, unacceptable adverse event, or subject decides to withdraw from the study. Overall study duration is projected to be 5 years.

6.1.1 CTEP IND Agents

6.1.1.1 Nivolumab

Nivolumab is to be administered as an approximately 30-minute IV infusion (duration may be modified per institutional guidelines), using a volumetric pump with a 0.2/1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for

delivery but the total infusion volume must not exceed 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.

6.1.1.2 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, or nutritional supplements that are known to interact with XL184 (cabozantinib) are not allowed during this study. 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.

6.2 Definition of Dose-Limiting Toxicity

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
≤1 out of 3	The dose level cohort will be expanded to 6 patients
≤1 out of 6	The dose will be considered as the dose for the expansion cohort.
≥2	This regimen will be considered unworthy for further development and the study will be closed. If 2 DLTs are experienced at the first cohort, one dose level de-escalation (Dose Level -1, cabozantinib 20mg daily) will be permitted

Dose-limiting toxicity (DLT) will be defined as any treatment-related grade 3 or 4 non-hematologic toxicity during the first cycle of therapy, including grade 3 nausea and/or vomiting and grade 3 diarrhea despite prophylaxis and/or treatment or any of the following grade 4 hematologic toxicities during the first cycle of therapy: thrombocytopenia and neutropenia of more than 7 days duration, neutropenia of any duration with fever or documented infection; additionally, treatment delay of 14 days or greater during Cycle 1 due to unresolved toxicity will be considered a DLT.

6.3 Dose Expansion Cohorts:

Once the study dose is established as safe in the patient population, 12 additional patients with KS would be enrolled. For the expansion cohort, patients will continue to be monitored for occurrence of DLT. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of nivolumab and XL184 (cabozantinib) with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

6.4.1 XL184 (Cabozantinib)

6.4.1.1 Anticancer Therapy

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

6.4.1.2 Other Medications

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

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

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

No concurrent investigational agents are permitted.

6.4.1.3 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, rifampentin, 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.

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 (IC50 = 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, emtricitabine.

Protein bound:
XL184 (Cabozantinib) is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 (Cabozantinib) with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and 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 Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions; therefore, XL184 should be taken on an empty stomach (fasting isrequired 2 hours before and 1 hour after each XL184 dose).

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with nivolumab and XL184 (cabozantinib) may continue up to 1 year, or 1 year after a partial response is achieved, or 6 months after a complete response is achieved until one of the following criteria applies

- Disease progression
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- •General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- 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

When one drug is held due to protocol-defined toxicity, both drugs should be held until improvement of events to the grade permissible for treatment resumption as per detailed dose modification guidelines in section 7 (for example, tolerable cabozantinib-related grade 2 hypertension and grade 2 hand-foot syndrome). In cases when dose modification guidelines call for permanent cessation of either nivolumab or XL184 (Cabozantinib) and the adverse event is a class-specific adverse event as highlighted in section 7, the alternate drug can be continued as per investigator’s discretion.

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

6.6 Duration of Follow-Up

Patients will be followed for 16 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

7. DOSING DELAYS/DOSE MODIFICATIONS

Toxicity evaluation will be done monthly for as long as the patient is on active treatment.

Complete blood counts with differential, comprehensive metabolic panel, and TSH will be done the beginning of each treatment cycle.

XL184 (cabozantinib) and nivolumab have class-specific safety profiles based on their mechanisms of action, but may also cause AEs that overlap. The management of these toxicities generally includes holding drug for moderate (Grade 2) toxicities and using systemic immunosuppression for severe (Grade 3/4) or prolonged moderate (>1 week) toxicities per the treating clinician's discretion as guided by the package insert of the respective drugs. Additional immunosuppression (e.g., anti-TNFα therapy, infliximab) may be used if IV steroids are ineffective at the discretion of the treating clinician using the package insert as a guide. When one drug is held both drugs should be held.

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, proteinuria, thrombosis and hand-foot syndrome. Examples of immune-related AEs caused by nivolumab are pneumonitis and endocrinopathies. For AEs without clear attribution to either component of study treatment or overlapping AEs, management of toxicity should include dose modifications of XL184 (cabozantinib) and immunotherapy, at the discretion of the investigator. Examples of overlapping AEs are GI hepatotoxicity, diarrhea, andrash. If the clinical course follows the pattern for one agent that guideline should be followed. For example, diarrhea that responds to holding the agents within 5-7 days without steroids and negative colonoscopy, proteinuria without renal impairment may follow the cabozantinib guidelines for dose reduction at the discretion of the investigator. If either drug may be involved the most stringent guideline should be followed. Patients who experience a Grade 3 or greater toxicity that is attributed to study medication and cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to Grade 2 or lower. Patients may subsequently be re-started on study drug, including at a reduced dose in the case of XL184 (cabozantinib).

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 Dose interruptions and/or reductions should be implemented for unacceptable toxicity.

- 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.
- XL184 (Cabozantinib) should be held for 2 days (48 hours) prior to any biopsy procedure, and may be resumed 2 days (48 hours) following the procedure, unless there isevidence 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 >4 consecutive weeks, XL184 (Cabozantinib) should be discontinued. In this situation, a patient may continue to receive Nivolumab per the discretion of the investigator.
- 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.

Many AEs can occur early (within the first few weeks) in the course of treatment, as XL184 (Cabozantinib) is expected to reach steady state exposure at approximately 2 weeks following the first dose. 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).

AEs 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.

AEs 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. Although unlikely based on the data from previous and ongoing studies, a dose reduction (dose level -1) at 20mg daily Cabozantinib for the first 6 patients in the run-in phase is permitted, and the subsequent dose at the expansion cohort will be adjusted accordingly. Dose delays will not be allowed in the safety run-in phase, and will be limited to the expansion phase.
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

Note:
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.Although unlikely based on the data from previous and ongoing studies, a dose reduction (dose level -1) at 20mg daily Cabozantinib for the first 6 patients in the run-in phase is permitted, and the subsequent dose at the expansion cohort will be adjusted accordingly

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 deemedsafe 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 grade1 (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 Adverse Events

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 ismanageable 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 supportivecare.
Grade 2 AEs which are intolerable to the patient, deemed unacceptable in the treating physician's judgment, recur after previously improving to ≤ grade 1, 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 within24 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. If this is a recurring AE, reduce the XL184 (Cabozantinib) dose by one level.
Grade 3 AEs that occur despite optimal prophylaxisor are not easily managed by medical intervention	Hold XL184 (Cabozantinib) until recovery to ≤ grade 1 or baseline, then resume at one dose level lower.
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 ata 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 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 asred blood cell transfusions should be managed according to institutional guidelines.

Other Hematological AEs	**Recommended Guidelines for Management**
Grade 4	Permanently discontinue XL184 (Cabozantinib) therapy unlessthe 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-abdominalabscess;
- 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).

Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with XL184 (Cabozantinib). After starting XL184 (Cabozantinib), subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula are present. 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 continuousoral 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 perianalregion 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 beavoided. 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 andalcohol 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. IfLFTs 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 beresumed 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 aone dose level reduction.
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 elevationof 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 4 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) therapymust be discontinued.

7.1.3.3 Pancreatic conditions

Asymptomatic Lipase or Amylase Elevations	**Intervention**
Grade 1 or **Grade 2**	Continue at current dose level. More frequent monitoring is recommended.
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 levelshave 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 4 weeks. If XL184 (Cabozantinib) is resumed at the samedose following a grade 4 lipase or amylase elevation and grade 3or 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 occurswithin 4 weeks.

Grade 4	Permanently discontinue XL184 (Cabozantinib) therapy. However, if the patient was unequivocally deriving benefit fromXL184 (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).

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 thatpatients 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.

7.1.3.4 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.

7.1.3.5 Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per

localapplicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued. See Section 7.2 for additional restrictions on anticoagulation therapy.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment.

Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI,cerebral infarction, or any other clinically significant arterial thromboembolic complication.

7.1.3.6 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 doseof 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 oneweek (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,,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.
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 kidneydamage).

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.

7.1.3.7 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 tovasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton glovesand 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 dailyand 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 theirtreating physician immediately if severity worsens.
Grade 2	XL184 (Cabozantinib) may be continued at the same dose levelif 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 potencysteroid 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 whentreatment 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 themanagement 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 lowerupon resolution to ≤ grade 1. Permanently discontinue XL184 (Cabozantinib) therapy if PPES worsens or does not improve within 4 weeks.

7.1.3.8 Osteonecrosis

Osteonecrosis has been reported in subjects 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.

Perform an oral examination prior to initiation of XL184 (cabozantinib) and periodically during XL184 (cabozantinib) treatment. Advise subjects regarding oral hygiene practice and to quickly report symptoms to Investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with XL184 (cabozantinib) should be interrupted for at least 3 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Withhold XL184 (cabozantinib) for development of ONJ until complete resolution.

7.1.3.9 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 subject is being treated with XL184 (cabozantinib). If dehiscence occurs, XL184 (cabozantinib) treatment should not be restarted until complete healing has taken place.
Treatment with XL184 (cabozantinib) should be stopped at least 3 weeks prior to elective surgery. Do not administer XL184 (cabozantinib) for at least 2 weeks after major surgery anduntil complete wound healing.

7.1.3.10 Proteinuria

Proteinuria has been reported with XL184 (Cabozantinib). Proteinuria should be monitored by measuring Urine protein/creatinine ratio (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 ≤2.5 mg/mg (>113.1 and ≤282.8 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 ≤2.5 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.
>2.5 and <3.5 mg/mg (>282.8 and <395.9 mg/mmol)	Dose reduce or hold XL184 (Cabozantinib). A nephrology consultation is recommended. 24-hour urine protein assessment must be sent off within 7 days. Continue to check UPCR again within 7 days, and repeat once a week until UPCR decreases to ≤2.5 mg/mg. Resume XL184 (Cabozantinib) at 1 dose level lower once UPCR is ≤2.5 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 ≤2.5 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 ≤2.5mg/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 <2.5 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 clinicallyindicated.

7.1.3.11 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.

7.1.3.12 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.

7.1.3.13 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

7.1.3.14 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.

7.1.3.15 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

7.2.1 Other Events

All Other Events	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below).

Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Off protocol therapy.
Recommended management: As clinically indicated	

Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment

Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment does not require discontinuation.

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

7.2.2 Skin Rash and Oral Lesions

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

7.2.3 Liver Function

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**

≤ Grade 1	Hold at investigator discretion until ULN or baseline. Resume at samedose level.
Grade 2	Grade 2 (3 × UNL to 5 × UNL): Hold until grade 1 (UNL-3 × UNL) orbaseline. Resume at same dose level at investigator discretion.
Grade 3	Grade 3 (5 × UNL to 20 × UNL) Hold until grade 1 or baseline. Resumeat same dose level at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If persistent or steroids are required, off protocol therapy.
Grade 4	Off protocol therapy.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (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. Please note: Grades for liver function follow UNL rather than multiples of baseline.	
Recommended management: see Hepatic AE management algorithm in Appendix E	

7.2.4 Diarrhea

Diarrhea /Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until baseline. No change in dose.
Grade 2	Hold until baseline. No change in dose.
Grade 3	Resume at same dose level at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. Ifpersistent or steroids are required off protocol therapy.
Grade 4	Off protocol therapy.
See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated afterresolution. Patients who require systemic steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

7.2.5 Pancreatic Disorders

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**

≤ Grade 1	Continue at same dose level if asymptomatic at investigator discretion.
Grade 2	Continue at same dose level if asymptomatic at investigator discretion. If symptomatic, resume at same dose level when resolved
Grade 3	Continue at same dose level if asymptomatic at investigator discretion.Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients whodevelop diabetes mellitus should be taken off treatment.
Grade 4	Hold until grade 2. Resume at same dose level if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus shouldbe taken off treatment.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm.	

7.2.6 Pneumonitis

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off protocol treatment.
Grade 4	Off protocol therapy.

Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.
Recommended management: See Pulmonary AE Management Algorithm

7.2.7 Other GI Disorders

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

7.2.8 Fatigue

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

7.2.9 Neurologic Events

Neurologic events	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with nochange in dose when resolved to baseline.

Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume atsame dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	
Recommended management: See Neurologic AE Management Algorithm	

7.2.10 Endocrine Events

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
≤ Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency orhypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 4	Off protocol therapy.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are noother associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy ofany kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	

7.2.11 Renal Disorders

Renal	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.

Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation overthe course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

7.2.12 Infusion Reaction Events

Infusion reaction	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation overthe course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

7.2.13 Fever

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

7.2.14 Cardiac Events

Cardiac*	**Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities**
Less than grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop

	then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off protocol treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

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

Prior to starting new corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, Cortrosyn® adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and thyroxine (T4) is recommended to 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 atany time it is clinically indicated.

Any patient started on corticosteroids initially, who is determined to not require steroid treatment for an autoimmune AE, may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent(s)

8.1.1 XL-184 (Cabozantinib) (NSC#761968)

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

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

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: C28H24FN3O5.C4H6O5 M.W.: 635.6 Daltons (L- malate salt)

Mode of Action: XL184 (Cabozantinib) inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are VEGFR3, RET, AXL, KIT, TIE-2, FLT-3, ROS1, and RON.

How Supplied: Exelixis supplies and the PMB, CTEP, DCTD, NCI distributes XL184 (Cabozantinib) tablets. The composition of the tablets is listed in the table below. The yellow film-coated tablets are available in the following free-base equivalent strengths and bottle configurations:

- 20 mg: round (5.6 mm); 30 tablets per HDPE bottle

XL184 (Cabozantinib)Tablet Components and Composition

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

Storage: Store intact bottles at controlled room temperature 200 C to 250C (680 F to 770 F); temperature excursions are permitted between 150 C and 300 C (590 F to 860 F) [see USP Controlled Room Temperature].
If a storage temperature excursion is identified, promptly return XL184 (Cabozantinib) to 200 to 250C (680 to 770 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 dispensingbottle).

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 approximately at the same time each day. Do not crush or chew. Do not take 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, rifampentin, phenobarbital, and St. John's Wort while taking XL184 (Cabozantinib). Avoid chronic use of strong CYP3A4 inhibitors suchas ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications.

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

XL184 (Cabozantinib) is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsomal (HLM). IC50 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.

<u>P-glycoprotein/ MRP2:</u>

In vitro data indicate that XL184 (Cabozantinib) is an inhibitor of P-glycoprotein transport activity (IC50 = 7.0 μM). Co-administration of XL184 (Cabozantinib) with a P-gp substrate mayresult 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, emtricitabine.

Protein bound:

XL184 (Cabozantinib) is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 (Cabozantinib) with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and 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 Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions; therefore, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each XL184 dose).

Patient Care Implications: Women of childbearing potential must use highly effective contraception while receiving XL184 (Cabozantinib) and for 5 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 7 months after the last dose.

Availability

XL-184 (Cabozantinib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

XL-184 (Cabozantinib) is provided to the NCI under a Collaborative Agreement between the

Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

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-1MAbM.W.: 146,221 Daltons
Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD- L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreignantigens 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 and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When 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 (eg, 240 mg, 360 mg, or 480 mg flat dose), Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total
volume 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°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to 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 IVpush or bolus injection.

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

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

Patient Care Implications:

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

Availability

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

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents

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.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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.

8.1.3.2 Agent Inventory Records

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

8.1.4 Investigator Brochure Availability

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

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The primary objective is to determine the safety of combined nivolumab and XL184 (cabozantinib) in HIV patients with advanced solid tumor, specifically in HIV patients with KS. Independent data from previous and ongoing studies have suggested a combination dose schedule. We can apply this information to evaluate combination doses with the expectation of limited cross-over toxicity and thereby anticipate that following a short run-in phase, we will be able to continue in the feasibility expansion portion.

Patient accrual will include HIV patients with advanced solid tumors, with ECOG performance status 0-1. Each cycle of treatment consists of 28 days. A two-week period of "priming" XL184 (cabozantinib) alone will be administered prior to Cycle 1 of combined XL184 (cabozantinib) /nivolumab. DLTs will be defined during Cycle 1 of therapy. All treatment is planned to be administered on an outpatient basis. Although unlikely based on the data from previous and ongoing studies, a dose reduction (dose level -1) at 20mg daily Cabozantinib for the first 6 patients in the run-in phase is permitted, and the subsequent dose at the expansion cohort will be adjusted accordingly. Dose delays will not be allowed in the safety run-in phase, and will be limited to the expansion phase.

The combination of nivolumab and XL184 (cabozantinib) will be examined in patients on ART regimens including drugs inducing or non-interacting with CYP3A4. The proposed dosing of XL184 (cabozantinib) for this trial is 40 mg daily based on the preliminary results of previous studies, especially AMC-087. Based on preliminary results of AMC-095, the nivolumab dosing schedule is recommended to be 480 mg every 4 weeks. Thus, for the current study, we propose nivolumab 480 mg every 4 weeks and XL184 (cabozantinib) 40 mg daily. This is also the dose regimen used in several ongoing NCI studies. We will only enroll patients on ART regimens including drugs inducing or non-interacting with CYP3A4 (patients taking potent CYP3A4 inhibitors will be excluded).

The criterion for declaring "safety" of the combination regimen based upon the 6-patient safety run-in will be observation of no more than one patient with DLT among these 6 patients.

9.2 Sample Size/Accrual Rate

Six patients will be enrolled in the safety run-in cohort. As many as possible KS patients will be included in the safety run-in cohort. The expansion phase will be limited to KS patients, and an additional 12 patients will be enrolled for the expansion cohort. Patients will be accrued at a rate of 1-1.25 per month.

Feasibility will be declared if at least 9 (75%) of the 12 KS patients in the expansion cohort are observed to complete at least 4 cycles that would yield 80% power to detect a true >4-cycle completion rate of 80% with 0.93 likelihood of rejecting feasibility for a true >4-cycle completion rate of 50%.

PLANNED ENROLLMENT REPORT

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
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
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	3	0	0	6
White	3	3	3	3	12
More Than One Race	6	6	3	3	18

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9.3 Analysis of Secondary Endpoints

Descriptive statistics (mean, median) will be computed at each assessment time point for each endpoint, including participants' immune status (CD4 and CD8 cell counts) and HIV viral loads. Changes in endpoint at each time point from baseline will be analyzed using paired nonparametric Wilcoxon sign-rank tests or paired t-tests in exploratory analyses.

9.4 Analysis of Exploratory Endpoints

Descriptive statistics (mean, median) will be computed at each assessment time point for each endpoint, including serum markers of immune activation- immune cell subsets and cytokine levels; tumor assessment of immune checkpoints (PD-L1, B7x, B7-H3, HHLA2), infiltrating immune cells and angiogenesis markers. Changes in endpoint at each time point from baseline will be analyzed using paired nonparametric Wilcoxon sign-rank tests or paired t-tests in exploratory analyses.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

following list of AEs (Section 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.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 3219 patients. Below is the CAEPR for XL184 (Cabozantinib).

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

Version 2.4, December 17, 2018[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	

		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		

Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
	Voice alteration		***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

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

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula,

Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis);

Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death **NOS;** Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of

any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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

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 2.5, June 10, 2023[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)***
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)	
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 opthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	
	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)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (Immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	

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%)**	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, 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 lymphocytes 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)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	

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%)**	
		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-related nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[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)***
		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.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website 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.
  - *[Include if protocol-specific expedited reporting exclusions will be made]*Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

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

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://ctepcore.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.4).

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

10.3.2 Rave-CTEP-AERS Integration

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

expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

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.

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. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

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 direct link from Medidata Rave.

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

- Study specific documents: Protocols > Documents> Protocol Related Documents> Adverse Event Reporting; and

- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

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

10.3.3 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.

10.3.4 Expedited Reporting Guidelines

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

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. 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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1. Death
2. A life-threatening AE
3. An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

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

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

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

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

Expedited AE reporting timeframes are defined as:

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

1SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

2For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

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.**

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**. 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 2 week prior to start of protocol therapy. Scans and x-rays must be done <4 weeks prior to the start of therapy. For patients with KS, the Baseline KS Assessment will be completed by the treating physician within 4 weeks prior to start of protocol therapy. Beginning C1D1 and onward, participants will be evaluated using the Overall KS Response Assessment every 8 weeks (+/- 4 weeks) until the off-study visit. 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.

			Cycle 1				**Cycle 2**				**Cycle 3**				**Cycle 4**	**Cycle 5**	**Cycle 6+$_p$**	
	Pre-Study	**Day -14**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 17**	**Wk 21**	**Off Studyc**
Nivolumaba			X				X				X				X	X	X	
XL184(cabozantinib): [b]		X ---X		X														
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X		X		X													
Physical exam	X	X	X		X		X		X		X				X	X	X	X
Vital signs[g]	X	X	X		X		X		X		X				X	X	X	X
Height	X																	
Weight	X	X	X		X		X		X		X				X	X	X	X
Performance status[d]	X	X	X		X		X		X		X				X	X	X	X
CBC w/diff, plts	X	X	X		X		X		X		X				X	X	X	X
Comprehensive Chemistry Panel[c]	X	X	X		X		X		X		X				X	X	X	X
Adverse event evaluation			X----------														-X	X
Tumor measurements[l]	X	Tumor measurements are repeated every 8 weeks (2 cycles) ± 7 days (not including the priming period). Documentation (radiologic) must be provided for patients removed from study for progressive disease.																X

Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks (2 cycles) ± 7 days (not including the priming period).																X
Photographs of KS Lesions	X	Photographs of lesions should be taken at the time of maximum response																X
Pregnancy test[f]	X																	
Urine Dipstick or UAh	X	X	X				X				X				X	X	X	X
ECG[i,O]	X	X	X				X				X				X	X	X	X
PT/INR, PTT	X										X							X
TSH, free T4	X		X				X				X				X	X	X	X
Amylase and Lipase	X	X	X				X				X				X	X	X	X
CD4+and CD8+ Lymphocyte Counts and HIV Viral Loadj (mandatory)	X		X								X m					X n	X	X
Troponin CK [o]	X																	
ECHO cardiogram o	X																	
XL184 (Cabozantinib) diaryk		X	X				X				X				X	X	X	X
Latent HIV Reservoir (optional)	X										X m					X n		X
Immune cell subset activation blood collection (optional)	X										X m					X n		X
Cytokine blood collection (optional)	X										X m					X n		X
Archival Tumor specimen (optional)	X																	

a: Nivolumab: infused every 4 weeks (-3 days, + 1 week). The maximum duration of treatment with nivolumab is 2 years.
b: XL184(cabozantinib): must be taken once daily on an empty stomach. Participants must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Participants should be instructed to take their XL184 (cabozantinib) dose at approximately the same time every day. If a participant 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. Treatment should begin on Day -14, then daily every 4 weeks (-3 days, + 1 week).
c: Off-study evaluation. Participants will be followed for 16 weeks from the date of study discontinuation or until toxicity resolution, whichever is later. Toxicity resolution may be monitored by the local site personnel via telephone contact with the participant.
d: Note: Performance status evaluations are based on a 4-week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.
e: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium . Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values.
f: Women of childbearing age must have a negative pregnancy test within 72 hours of first treatment.
g: If hypertension (BP 140/90) is observed, decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.
h: Proteinuria seen on urine dipstick or UA should warrant urine protein/creatinine ratio (UPCR) determination and management.
i: ECG and QTc assessments will be performed at within 4 weeks prior to start of therapy , baseline, day -14, C1d1, and day 1 of all subsequent cycles. Additional ECGs will be performed as indicated
j: CD4+ and CD8+ Lymphocyte Counts and HIV viral load will be obtained locally at within 2 weeks prior to the start of therapy, at baseline, day 1 of cycle 1, day 1 of cycle 3, day 1 of cycle 5, every 12 weeks during protocol participation, and at time of treatment discontinuation.
k: Collection of XL184(cabozantinib) drug diary from previous cycle and distribution of new diary. Collect final diary at treatment discontinuation
l: CT scan for tumor measurement performed after every 2 cycles (every 8 weeks) of therapy for participants with solid tumors. Participants with KS will not require CT scans. m: This time point is day 1 of cycle 3 prior to treatment.
n: This time point is day 1 of cycle 5 prior to treatment.
o: Any patient with a history of CHF or at risk because of underlying cardiovascular disease or previous exposure to cardiotoxic drugs as clinically indicated. p: D1C6 and all D1 subsequent cycles

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 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 Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur* J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with XL184 (Cabozantinib) and Nivolumab

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

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

12.1.2 Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in **millimeters** (or decimal fractions of centimeters).

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

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymphnode must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest

diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

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.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using

calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease.

Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

Tumor Markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and

PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

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

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions,

taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

12.1.5 Duration of Response

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

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

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

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.

12.2 Other Response Parameters

12.2.1 Tumor Proportion Score (TPS)

PD-L1 IHC protein expression will be determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells with partial or complete membrane staining. A specimen should be considered PD-L1 positive if 50% or greater of the viable tumor cells (TPS >50%) exhibit membrane staining at any intensity (Garon *et al*., 2015); however, a different cut-off value of 1% or greater for PD-L1 positivity has been recently proposed (Herbst *et a*l., 2016). The stain was performed by using the PD-L1 IHC 22C3 pharmDx kit in accordance with the conditions specified by the manufacturer and all other applicable regulations. PD-L1 IHC 22C3 pharmDx is an FDA-approved qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1, clone 22C3 intended for use in the detection of PD-L1 protein expression

12.2.2 Combined Positive Score (CPS)

Given no established methodology for KS, PD-L1 IHC protein expression will also be determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen will be considered to have PD-L1 expression if CPS ≥1 (or adjust as per different tumor types, for instance, CPS ≥ 10 is considered positive in advanced esophageal squamous cell carcinoma).

12.2.3 AMC Kaposi Sarcoma Tumor Assessment:

The AMC Kaposi's Sarcoma Tumor Assessment Manual of Procedures (MOP) provides detailed instructions for KS response assessment requirements (Appendix H). Assessment of response to protocol therapy must be based on the KS Response criteria as indicated in the protocol. Photographs will be taken to assist in documentation of the diagnosis of KS and for clinical monitoring purposes. Patients must be consented to the photography.
Lesion photographs must be collected at baseline, at the time of initial and maximal response, and at the final participant visit (off study). See Appendix H (Section 2.0 – Photographic Record) for more details on how to take the photographs and save and store the images.

13. STUDY OVERSIGHT

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

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly conference calls with the Study Investigators [and, if needed, the CTEP Medical Officer(s)] to review accrual, progress, and adverse events and unanticipated problems.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

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.

13.1 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.

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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 email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. 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 eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; 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 replace the eLearning link 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 receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management 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 email at ctsucontact@westat.com.

13.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). 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.

13.1.2 Responsibility for Data Submission

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

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

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as

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

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).

13.2 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, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status 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, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.3 Collaborative Agreements Language

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

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13.4 Genomic Data Sharing Plan

N/A

13.5 Incidental/Secondary Findings Disclosure Procedure

N/A

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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APPENDIX C PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL 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 #:

Study Drug(S):

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

APPENDIX D PATIENT MEDICATION DIARY

CTEP-assigned Protocol # 10387
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – XL184 (Cabozantinib) – For Cycles 1+

Today's date: _____ **Agent: XL184 (Cabozantinib)**
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) at the same time each day:
   ☐ 2 (20 mg) tablets every day; (or) ☐ 1 (20 mg) tablet every day; (or) ☐ 1 (20 mg) tablet every other day.
   You should swallow the tablets as a whole. **Do not crush or chew**. You should take XL184 (Cabozantinib) on an empty stomach. Do not eat at least 2 hours before and 1 hour after taking XL184 (cabozantinib).
3. Store XL184 (Cabozantinib) tablets in the original bottle and not in weekly pill boxes. 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. You should not take the missed dose if it is within 12 hours of your next scheduled 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.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
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 tablets taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:_____

CTEP-assigned Protocol # 10387
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – XL184 (Cabozantinib) – For Cycles 1+

Today's date: _____ **Agent: XL184 (Cabozantinib)**
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) at the same time each day:
   ☐ 2 (20 mg) tablets every day; (or) ☐ 1 (20 mg) tablet every day; (or) ☐ 1 (20 mg) tablet every other day.
   You should swallow the tablets as a whole. **Do not crush or chew**. You should take XL184 (Cabozantinib) on an empty stomach. Do not eat at least 2 hours before and 1 hour after taking XL184 (cabozantinib).
3. Store XL184 (Cabozantinib) tablets in the original bottle and not in weekly pill boxes. 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. You should not take the missed dose if it is within 12 hours of your next scheduled 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.				
3.				
4.				
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27.				
28.				

Physician's Office will complete this section:

1. Date patient started protocol treatment _____

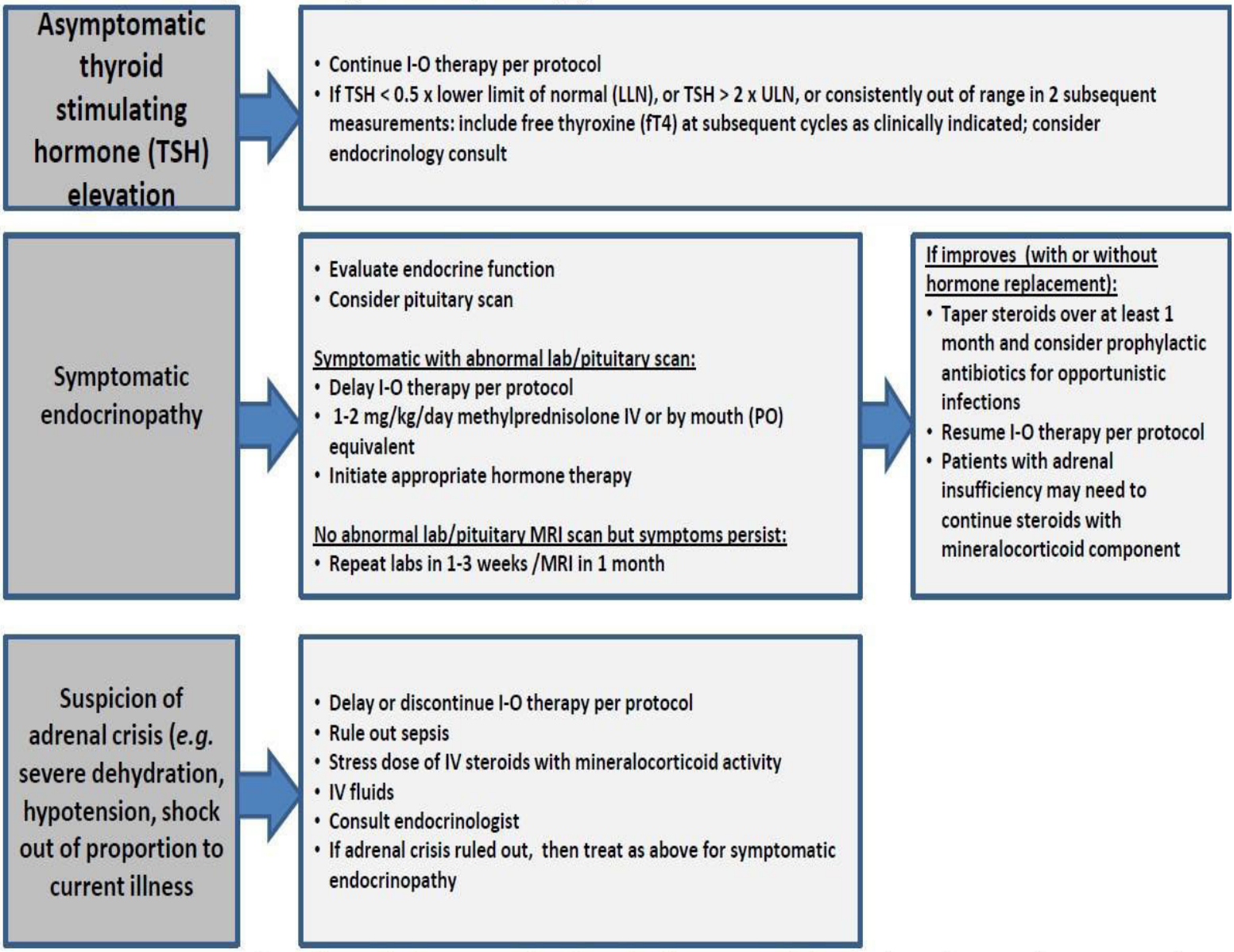
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of tablets taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:_____

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

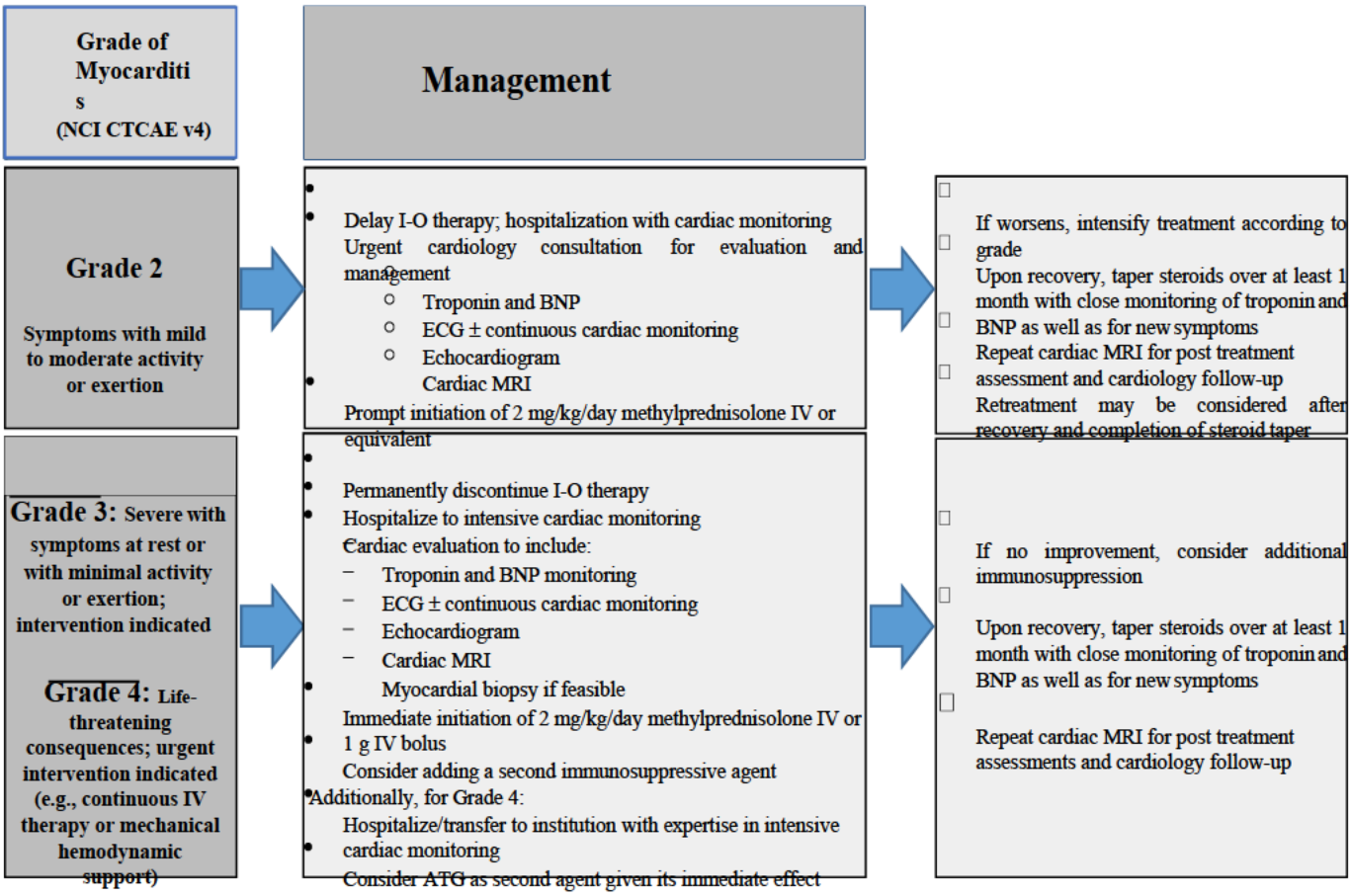
Endocrinopathy Management Algorithm

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



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

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

GI Adverse Event Management Algorithm

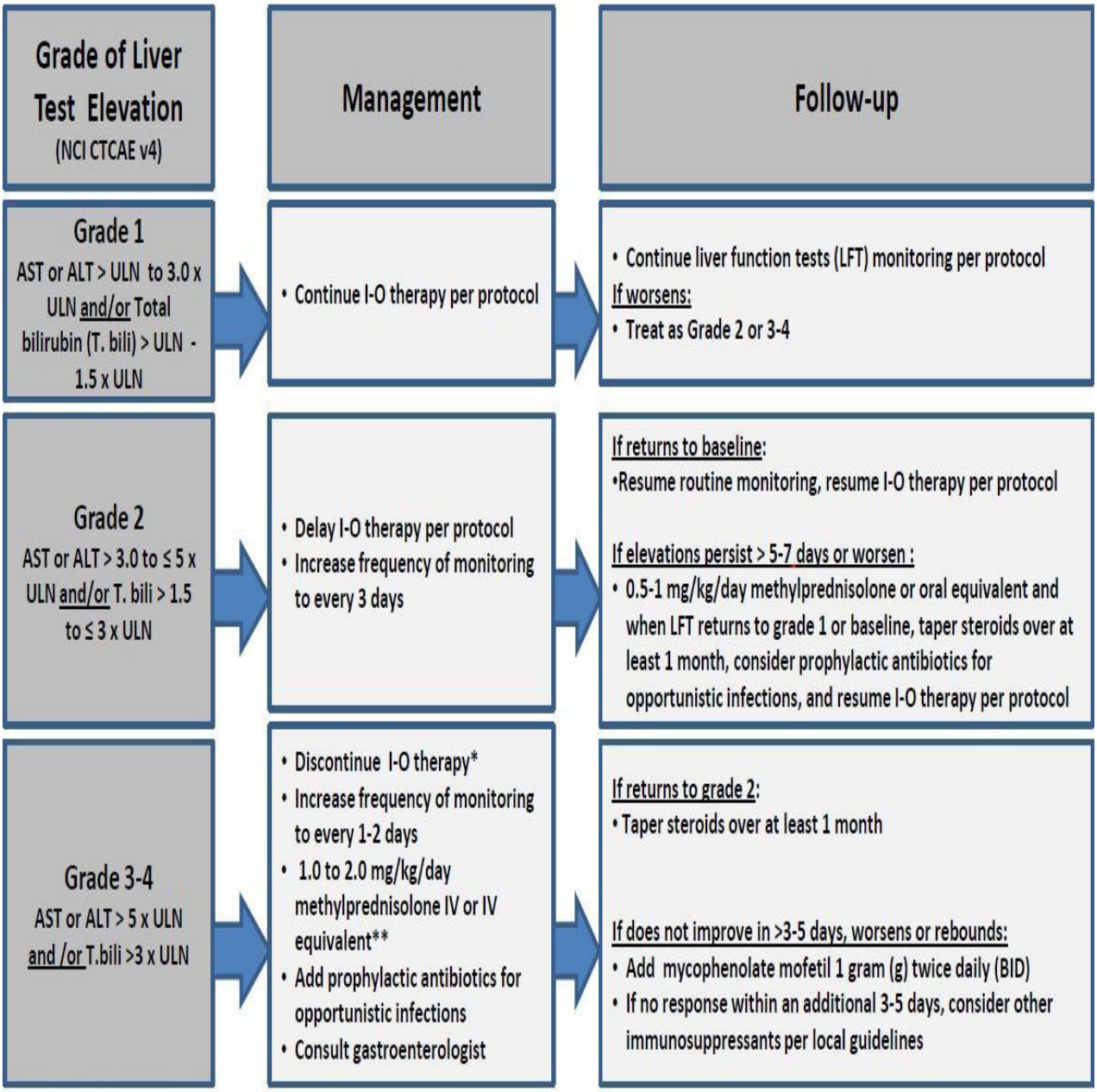
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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 (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (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 activities of daily living (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.

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

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

Neurological Adverse Event Management Algorithm

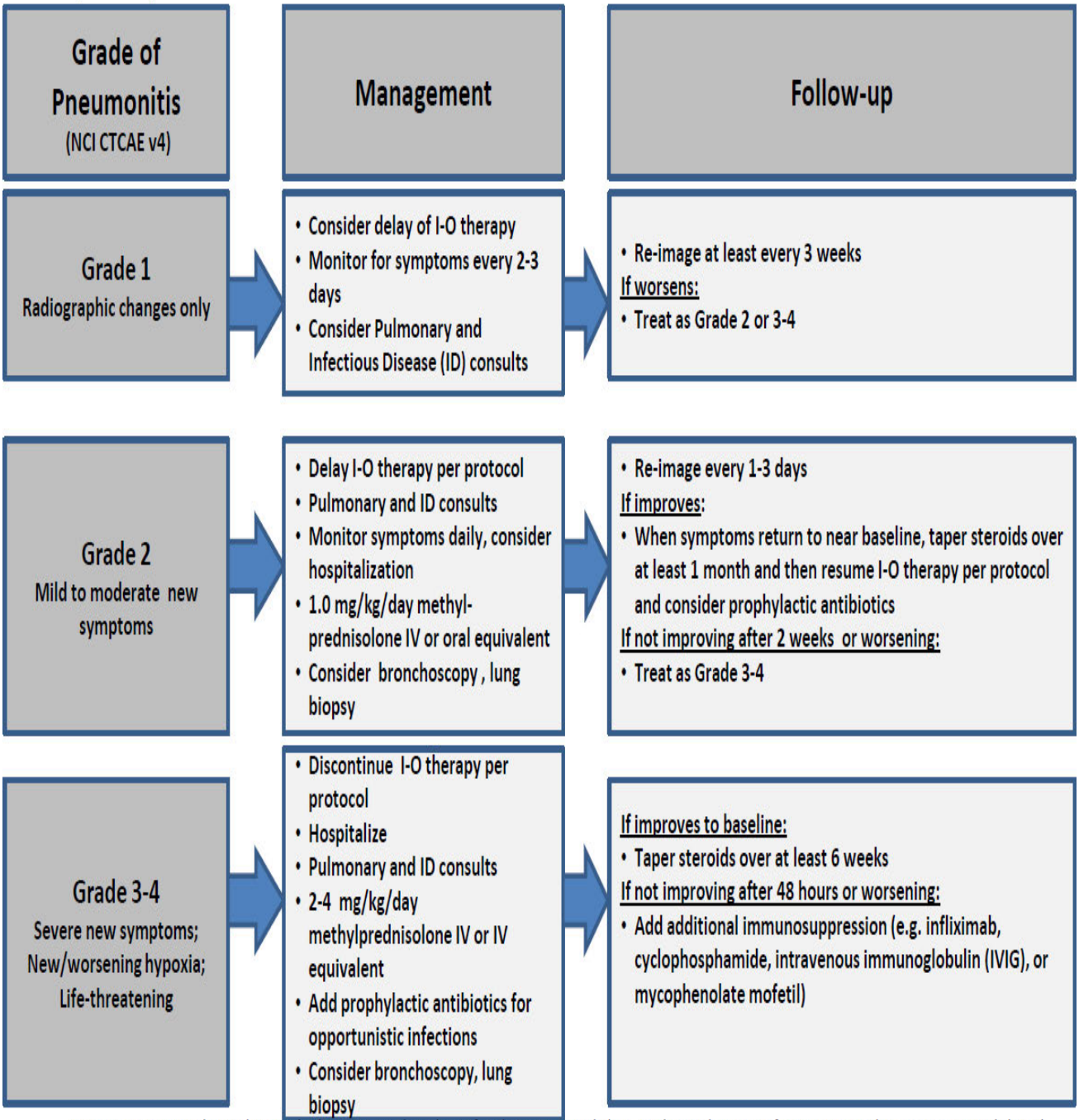
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

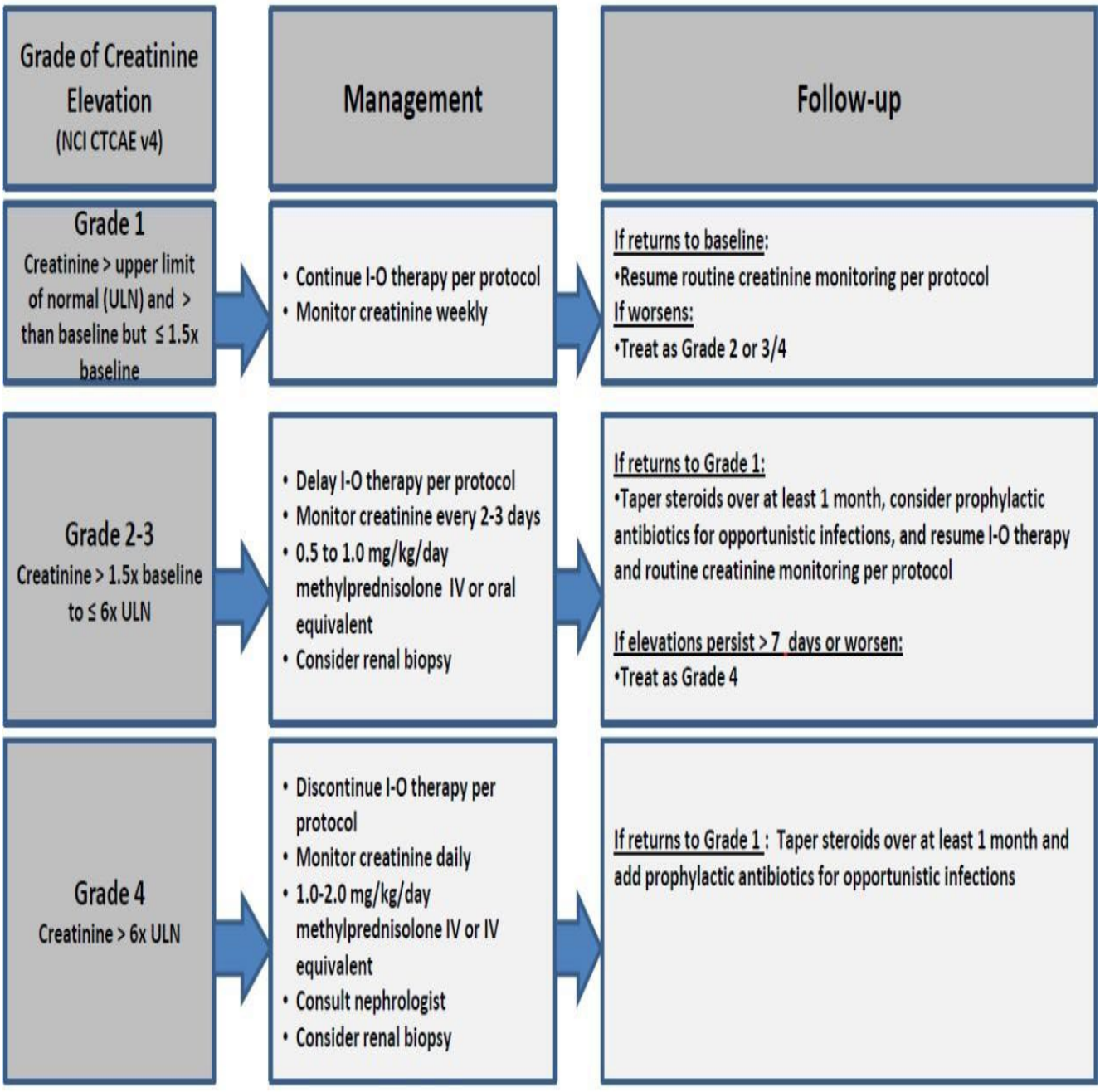
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

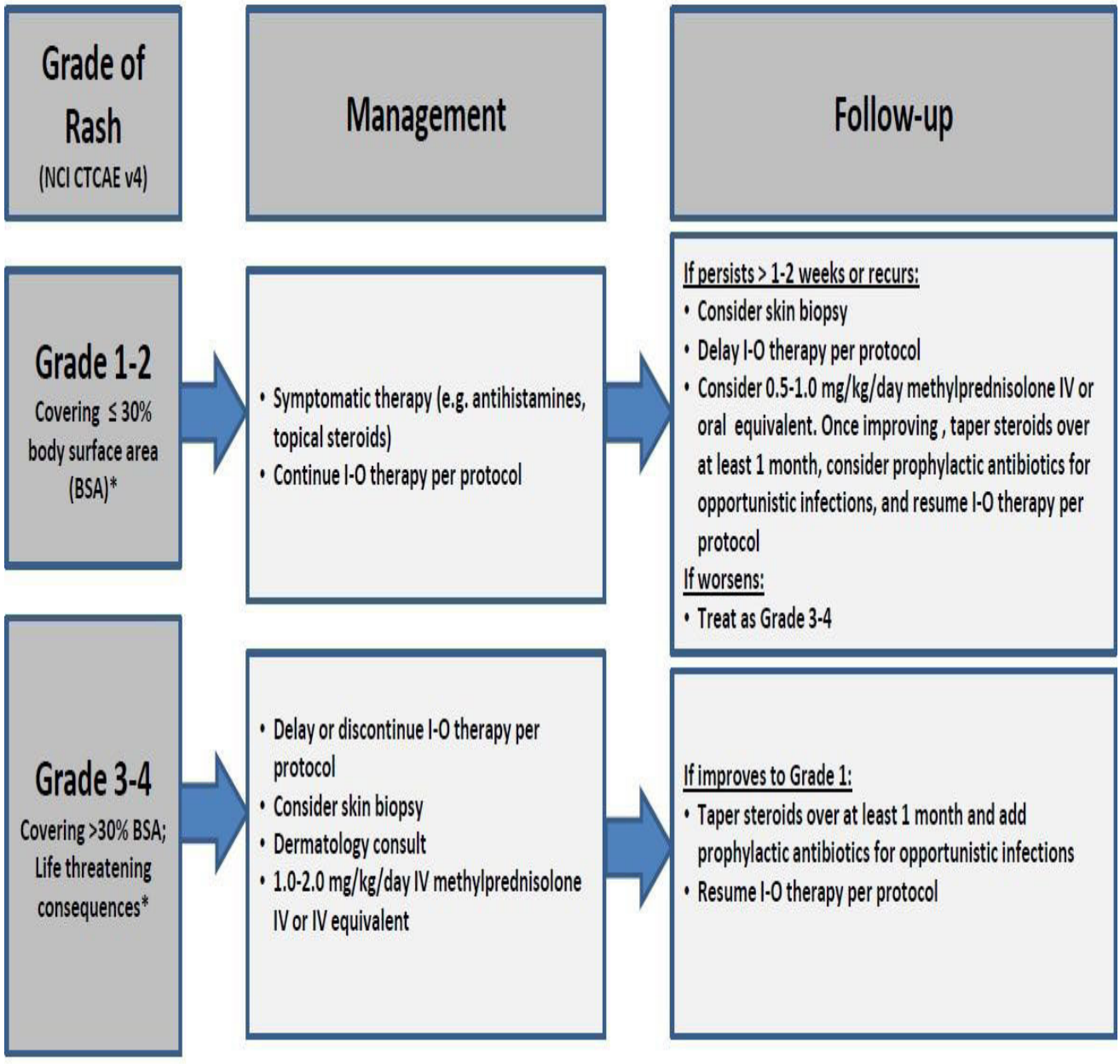
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Participant ID:_____-_____- _____
Date of evaluation:_____/_____/_____(DDMMMYYYY)
Visit 0

APPENDIX F BASELINE KS ASSESSMENT

Participant ID:_____-_____- _____
Date of evaluation:_____/_____/_____(DDMMMYYYY)
Visit 0

Baseline KS Assessment:

The AMC Kaposi's Sarcoma Tumor Assessment Manual of Procedures (MOP) provides detailed instructions for KS response assessment requirements. Assessment of response to protocol therapy must be based on the KS Response criteria as indicated in the protocol. Please see protocol and MOP for further guidelines on response evaluation.

KS Staging

1. KS Staging at registration:

   a. Tumor (T): *(check one)*
   - ☐ Tumor is confined to skin and/or lymph nodes and/or patient has minimal oral disease
   - ☐ Tumor with edema, ulceration, or extensive oral KS or gastrointestinal KS or KS in other nonnodal viscera

   b. Immune system (I): *(check one)*
   - ☐ CD4 cells greater than or equal to 200/uL
   - ☐ CD4 cells less than 200/uL
   - ☐ N/A

   c. Systemic illness (S):

History of opportunistic infection (OI) and/or thrush?	☐ Yes ☐ No
B-symptoms present?	☐ Yes ☐ No
ECOG > 1?	☐ Yes ☐ No
Other HIV-related illness (e.g., neurological disease, lymphoma)?	☐ Yes ☐ No

Identify and Measure Cutaneous Marker Lesions (MOP Section 1.1.1)

- Select bi-dimensionally measurable marker lesions for assessing changes in lesion dimensions. Select the largest lesions with clearly defined margins.
- Measure a minimum of 5 marker lesions that can be reproducibly measured at follow-up visits. If fewer than 5 bi-dimensionally measurable marker lesions are available, the total surface area of the marker lesion(s) must be ≥ 700mm^2.
- Ensure an additional two lesions (other than the marker lesions) are selected that are accessible for a punch biopsy.
- Take pictures:
  - Take close-up pictures of the marker lesions with a millimeter ruler; if there are multiple nearby lesions, take an orientation picture to clearly indicate which is the marker lesion among a group of lesions, thus helping to distinguish the lesion at future visits.
  - Take larger view pictures of the marker lesions to show the lesion's location on the body.
  - Take pictures of larger views of the back, chest, arms (front and back), legs (front and back), feet (including soles), whether involved in KS or not. In addition, photos should be taken of any other area with significant involvement at baseline (e.g. the face).
- To optimize reproducibility of accurately re-identifying and measuring change in lesions, when possible:
  - Choose lesions that are at least 10 x 10mm.
  - Choose lesions that are at least 10mm away from nearby lesions and are clearly distinguishable from nearby lesions (i.e. by shape, location).

MARKER LESIONS

Representative Area (choose from list below)[1]:	Specify Location within the Representative Area:	Dimension 1 (mm):	Dimension 2 (mm):	Area (mm^2):	Were close- up photos taken[2]?	Were larger view photos taken[2]?
1.					☐ Yes ☐ No	☐ Yes ☐ No
2.					☐ Yes ☐ No	☐ Yes ☐ No
3.					☐ Yes ☐ No	☐ Yes ☐ No
4.					Yes No	Yes No
5.					Yes No	Yes No
			Sum of the Areas:			

[1]**Representative area**:
2. Head
3. Neck
4. Chest
5. Abdomen
6. Whole back
7. Upper back
8. Lower back
9. Whole right arm (including upper & lower arm, excluding hand)
10. Upper right arm
11. Lower right arm
12. Right hand
13. Whole right leg (including upper & lower leg, excluding foot)
14. Upper right leg
15. Lower right leg
16. Right foot
17. Whole left arm (including upper & lower arm, excluding hand)
18. Upper left arm
19. Lower left arm
20. Left hand
21. Whole left leg (including upper & lower leg, excluding foot)
22. Upper left leg
23. Lower left leg
24. Left foot
25. Genital
26. Buttocks
27. Oral cavity

[2]**Photographs**:
Photographs are required for each marker lesion. The marker lesion(s) must be labeled in the photographs #1-#5, as applicable. Two photos will be taken for each lesion 1) A close-up of the lesion with a millimeter ruler to demonstrate the size of the lesion and 2) A larger view photo that shows the lesion's location on the body.

1. Were photographs of the following areas taken? *If no for any of the below areas, please document the reason why:*

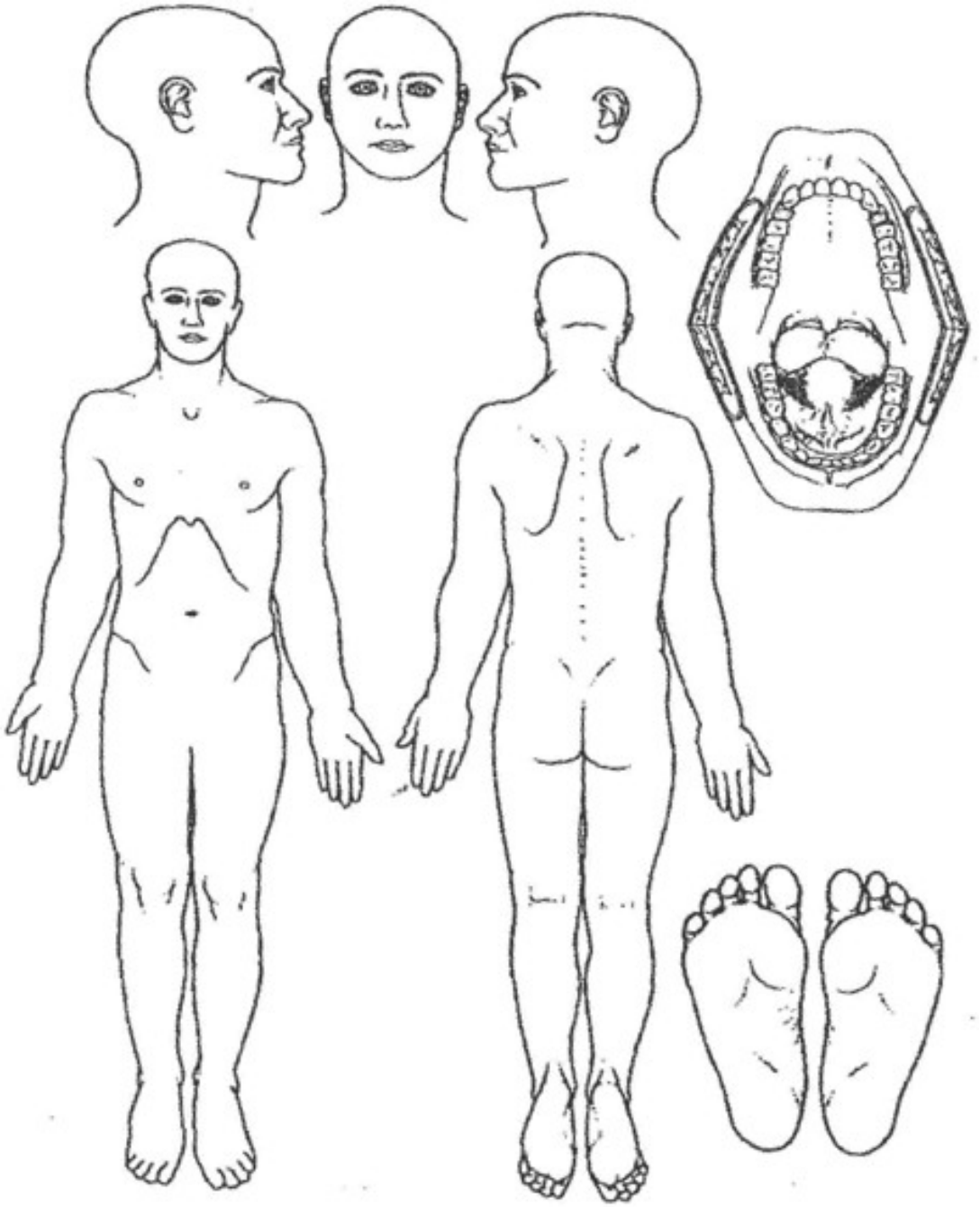
_____

Back: ☐ Yes ☐ No	**Front of legs**: ☐ Yes ☐ No
Chest: ☐ Yes ☐ No	**Back of legs**: ☐ Yes ☐ No
Front of arms: ☐ Yes ☐ No	**Feet** (including soles): ☐ Yes ☐ No
Back of arms: ☐ Yes ☐ No	**Other areas with significant involvement at baseline**: ☐ Yes ☐ No ☐ No other areas with significant involvement

2. Have all of the photographs been stored electronically?: ☐ Yes ☐ No

Photographs must be stored electronically under the participant ID number and back-up electronic storage will be kept. Only dedicated study staff and the sponsor should have access to the photographs. Please ensure no identifying information is included with the digital picture file.

- Use the KS Body Diagram to indicate the location of marker lesions; when lesions are a part of a cluster, indicate the position of nearby lesions on the diagram as well. Label the marker lesions #1-5 on the diagram.
- Identify the location of the lesions (other than the marker lesions) where biopsies were collected with an "x" on the diagram.
- *If the participant has > 50 lesions at entry*: Circle the location of the Representative Areas (A-C) selected in the table below and label A-C.



Evaluate Lesion Number (MOP Section 1.1.2)

How many lesions did the participant have? ☐ > 50 lesions ☐ ≤ 50 lesions

Participants with ≤ 50 total skin and oral lesions:

- **ALL** lesions must be evaluated for changes in number and characteristics. Select '1. Total body' as Representative Area A below.

Participants with > 50 total skin and oral lesions:

- Choose up to three representative areas (labeling A through C below) for evaluating change in lesion numbers and characteristics.
- It is preferable that each representative area should have at least five lesions, and the total number of lesions counted should be at least 20, if possible, for the evaluation of change in lesion numbers and lesion characteristics.
- If it is not practical to choose three representative areas, the number of areas selected is left to the investigator's clinical judgement.
- The total number of raised and flat lesions in the representative area(s) must be counted.
- Each representative area must be designated by the same letter (A-C) on subsequent evaluations (e.g. representative area 'A' at study entry must be recorded as 'A' at subsequent evaluations. Count only lesions in the areas selected at baseline for subsequent measurements.)

1. *Only for participants with > 50 cutaneous lesions*: Were photographs taken of each of the representative areas defined at study enrollment and used for clinical assessment of response?

☐ Yes ☐ No ☐ No, participant has ≤ 50 cutaneous lesions

	Representative Area A[1]:	**Representative Area B[1]:**	**Representative Area C[1]:**
Total number of raised lesions:			
Total number of flat lesions:			
Total number of lesions:			

[1]Representative area:
1. Total body
2. Head
3. Neck
4. Chest
5. Abdomen
6. Whole back
7. Upper back
8. Lower back
9. Whole right arm (including upper & lower arm, excluding hand)
10. Upper right arm
11. Lower right arm
12. Right hand
13. Whole right leg (including upper & lower leg, excluding foot)
14. Upper right leg
15. Lower right leg
16. Right foot
17. Whole left arm (including upper & lower arm, excluding hand)
18. Upper left arm
19. Lower left arm
20. Left hand
21. Whole left leg (including upper & lower leg, excluding foot)
22. Upper left leg
23. Lower left leg
24. Left foot
25. Genital
26. Buttocks
27. Oral cavity

Evaluate Edema (MOP Section 1.1.3)

1. Is there any tumor-associated edema at this evaluation?
   ☐ Yes No (*If No, provide measurements for the circumference of the ankle and calf and skip to "Perform*
   ☐ *Oral Examination)*

Periorbital/Scrotal/Genital Edema:		
Edema Site:	**Edema Present?**	**Characterization of Edema:**
Periorbital	☐ Yes ☐ No	If yes, describe severity: ☐ Swelling of the eyes noted occasionally or improves over the day ☐ Swelling of the eyes noted at all times but does not interfere with eyesight or function ☐ Swelling of the eyes noted at all times and interferes with eyesight or function sometimes ☐ Swelling of the eyes noted at all times and interferes with eyesight or function at all times
Scrotal/Genital	☐ Yes ☐ No	If yes, describe severity: ☐ Swelling of the scrotum noted occasionally ☐ Swelling of the scrota noted at all times but no interference with function ☐ Swelling interferes with urination, sexual function, withdrawing foreskin sometimes ☐ Swelling interferes with urination, sexual function, withdrawing of foreskin all of the time

Extremity Edema:		
Edema Site:	**Edema Present?**	**Circumference (cm):** ***REQUIRED FOR ALL PARTICIPANTS***
Right ankle	☐ Yes ☐ No	
Left ankle	☐ Yes ☐ No	
Right calf	☐ Yes ☐ No	
Left calf	☐ Yes ☐ No	
Right thigh	☐ Yes ☐ No	
Left thigh	☐ Yes ☐ No	
Right foot	☐ Yes ☐ No	
Left foot	☐ Yes ☐ No	
Right arm	☐ Yes ☐ No	
Left arm	☐ Yes ☐ No	
Right hand	☐ Yes ☐ No	
Left hand	☐ Yes ☐ No	
Other:	☐ Yes ☐ No	
Characterization of the participant's symptoms of extremity edema:	If the participant has edema in any extremity, describe severity: ☐ No symptoms ☐ Completely resolves with limb elevation and rings/shoes fit without difficulty ☐ Does not completely resolve with limb elevation or rings/shoes do not fit normally ☐ No improvement with limb elevation or reduced function	

Perform Oral Examination (MOP Section 1.1.4)

Oral Cavity:	
1. Was an oral mucosal tissue examination performed per the MOP?	☐ Yes ☐ No (*If No, answer Questions 2 and 3 and skip to "Evaluating Disease that Cannot be Measured".)*
2. Note the color, texture, and any surface abnormalities of the upper and lower lip:	• Color: • Texture: • Surface abnormalities:
3. Circle any abnormalities of the tongue:	• None • Swelling • Coating • Ulceration • Variation in size • Variation in color • Variation in texture • Other:
4. Are there any KS oral lesions present at this evaluation?	☐ Yes (*If Yes, Complete the "Oral Cavity Evaluation" source document.)* ☐ No

Evaluating Disease that Cannot be Measured (Evaluable Disease, Visceral KS) (MOP Section 1.1.5)

- Lesions considered non-measurable include: ascites, pleural or pericardial effusions, lymphangitic lung disease, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, bone metastases without an identifiable soft tissue component that can be evaluated by cross-sectional imaging techniques, and lesions that can only be identified by endoscopic, bronchoscopic, or laparoscopic techniques.

Pain Symptoms:	
1. Is the participant experiencing tumor-related pain?	☐ Yes ☐ No (*If No, skip to "Foot".)*
2. Anatomic site of <u>worst</u> pain:	
3. Is the participant on analgesics for tumor-related pain?	☐ Yes *(If Yes, enter a Concomitant Medication Form)* ☐ No
4. On a scale of 0 (no pain) to 10 (excruciating pain), what was the average pain experienced by the participant over the last 24 hours? *(circle one)*	0 1 2 3 4 5 6 7 8 9 10 Unknown

Foot:	
1. Are there any foot KS lesions present at this evaluation?	Yes No (*If No, skip to "GI Evaluation".)* If yes, specify physical findings:
2. Participant symptoms attributable to foot KS: *(check one)*	If the participant has foot KS lesions, describe severity: No symptoms or limitations related to KS Active but cannot perform more than normal activities Normal activities mildly limited Moderate impairment of activity Severe impact of activity

GI Evaluation:	
1. Was a radiographic, endoscopic, or other objective evaluation of the GI tract done at this visit?	Yes *(If "Yes", Complete the "GI Evaluation" source document.)* No
2. Participant GI symptoms **attributable to KS**: *(check one)*	No symptoms Mild GI symptoms Bleeding not requiring transfusion, pain not requiring analgesics, frequent GI symptoms Gross bleeding requiring transfusions, evidence of obstruction, unable to maintain adequate food intake with involuntary weight loss of > 5% from baseline, pain requiring analgesics

Pulmonary Evaluation:	
1. Was a radiographic or other objective pulmonary evaluation done at this visit?	Yes *(If "Yes", Complete the "Pulmonary Evaluation – Baseline" source document.)* ☐ No
2. Participant pulmonary symptoms **attributable to KS**: *(check one)*	☐ No symptoms ☐ Dyspnea on exertion ☐ Dyspnea on normal activity ☐ Dyspnea at rest requiring oxygen and/or hemoptysis

Other Sites for Evaluation:	
1. Was a radiographic or other objective evaluation for other visceral KS disease sites done at this visit?	☐ Yes *(If "Yes", Complete the "Visceral Disease – Other Sites Evaluation" source document.)* ☐ No

Comments:

Signature of Person Completing the Form (if not a CTEP-registered Investigator):

_____ Date:_____/_____/_____(DDMMMYYYY)

CTEP Investigator's Signature:_____Date:_____/_____/_____
(DDMMMYYYY)

APPENDIX GKS OVERALL RESPONSE ASSESSMENT

Overall KS Response Assessment:

The AMC Kaposi's Sarcoma Tumor Assessment Manual of Procedures (MOP) provides detailed instructions for KS response assessment requirements. Response must be based on the KS Response criteria as indicated in the protocol. Please see protocol and MOP for further guidelines on response evaluation.

Overall Response Assessment (MOP Section 1.3.4)

KS resolution or decrease must last for at least 4 weeks to be classified as confirmed CR or PR. This confirmed response is considered the "best response." Please note that "best response" may improve after the initial confirmed PR.

☐ **Progressive disease** *(Refer to table on page 14 of the MOP)*
If PD, first observation date:_____/_____/_____(DDMMMYYYY)
Progression/recurrence type:
☐ Cutaneous
☐ Noncutaneous
☐ Both cutaneous and noncutaneous

☐ **Stable disease** *(Participant does not meet the criteria for CR, PR, or PD)*

☐ **Partial response** *(Refer to table on page 13 of the MOP)*
If PR, first observed date:_____/_____/_____(DDMMMYYYY)
Confirmed? *(PR lasting at least 4 weeks)*: ☐ Yes ☐ No

Confirmed observed date:_____/_____/_____(DDMMMYYYY)

To be answered only after participant that has had confirmed PR: Has the participant had improvement since the initial confirmed partial response but has not met criteria for complete response?
☐ Yes *(If Yes, this is considered a new best response)*
☐ No *(If No, please evaluate protocol criteria for progressive disease (PD) or complete response (CR). If the participant does not meet criteria for either PD or CR, the participant should still be considered a partial response (PR).)*

Date of new best response:_____/_____/_____(DDMMMYYYY)

☐ **Complete response** *(Participant has shown the absence of any detectable residual disease, including tumor associated edema)*

- In some individuals, residual skin color changes may remain visible at one or more sites of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered PR.

To be answered only when residual macules that are slightly darker than the surrounding normal skin are present and the participant is otherwise believed to have a CR: Was a

confirmatory biopsy performed? ☐Yes ☐No

If CR, first observed date:_____/_____/_____(DDMMMYYYY)
Confirmed? *(CR lasting at least 4 weeks)*: ☐Yes ☐No

Confirmed observed date:_____/_____/_____(DDMMMYYYY)

To be answered only after participant that has had confirmed CR: Does the participant continue to meet protocol criteria for complete response?
☐Yes
☐No

Comments:

Signature of Person Completing the Form (if not a CTEP-registered Investigator):

_____ Date:_____/_____/_____(DDMMMYYYY)

CTEP Investigator's Signature:

_____ Date:_____/_____/_____(DDMMMYYYY)

APPENDIX H KS TUMOR ASSESSMENT MANUAL OF PROCEDURES

AIDS MALIGNANCY CONSORTIUM

AMC KAPOSI SARCOMA TUMOR ASSESSMENT MANUAL OF PROCEDURES

Provided by: AIDS Malignancy Consortium (AMC)
Kaposi Sarcoma Working Group

Version 1.0
July 19, 2018

TABLE OF CONTENTS

MANUAL OF PROCEDURE INSTRUCTIONS

This Manual of Procedures (MOP) is supplementary to all Kaposi sarcoma protocols. In any caseof discrepancy between the protocol and the MOP, the protocol must always been followed. Anyquestions regarding discrepencies or any other content from the MOP may be directed to the AMC ODMC at amcpm@emmes.com.

1.0 KS EXAM AND EVALUATIONS OF RESPONSE

1.1 Kaposi Sarcoma Entry Examination

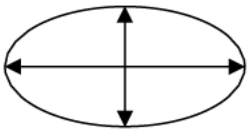
Timing - The KS entry examination may be performed on Day 0 prior to receiving study medication but no earlier than 7 days before initiating treatment. Tumor measurements should include the following:

i. Identify and measure cutaneous marker lesions

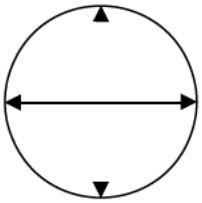
Select bi-dimensionally measurable marker lesions for assessing changes in lesiondimensions. Select the largest lesions with clearly defined margins. **When available, a minimum of five bi-dimensionally measurable KS cutaneousmarker lesions should be selected. If fewer than five bi-dimensionally measurable marker lesions are available, the total surface area of the markerlesion(s) must be ≥ 700mm².** To facilitate repeated lesion measurements, the location of each marker lesion should be recorded on a standard body diagram in relation to body landmarks and other nearby lesions and photographed as describedin Section 2 of this MOP. Additionally, the participant will need two lesions greateror equal to 4 x 4 mm that are accessible for 3-mm punch biopsy.

Measure marker lesions
Each marker lesion should be measured in millimeters, indicating the longest lineardimension and the longest dimension perpendicular to it. For this protocol, the product of the largest perpendicular diameters of the marker lesion will be considered the AREA of the marker lesion. Please refer to the diagrams below:

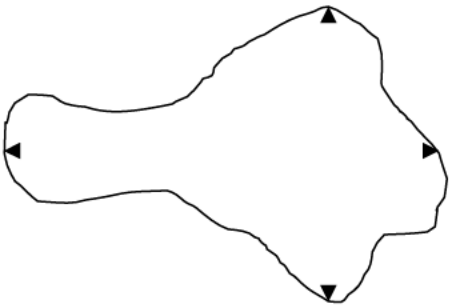
Calculating the **area** of the indicator lesions



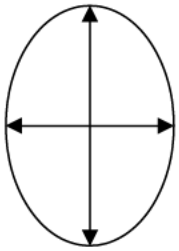
Oval Lesion: 35 mm X 16 mm = 560 mm²



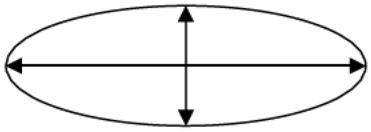
Round Lesion: 25 mm X 25 mm = 625 mm²



Irregular Lesion: 57 mm X 39 mm = 2223 mm²



Oval Lesion: 32 mm X 22 mm = 704 mm²



Oval Lesion: 47 mm X 16 mm = 752 mm²

Next, calculate the area of the indicator lesion**(**s**)**.

> To calculate the sum of the areas of the 5 example indicator lesions above, simply add the areas of each lesion:
>
> 560 mm^2 + 625 mm^2 + 2223 mm^2 + 704 mm^2 + 752 mm^2 = 4864 mm^2
>
> Using the five marker lesions above, the sum of the areas is 4864 mm^2

The sum calculated at entry or at the best response will be used to determine the response status at follow-up visits.

ii. Evaluate lesion number

For participants with ≤ 50 total skin lesions, all lesions must be evaluated for changes in number and characteristics. For participants with > 50 total skin lesions,choose three representative areas, if possible, for evaluating change in lesion numbers and characteristics (preferably each selected representative area should have at least five lesions, and the total number of lesions counted should be at least20). If it is not practical to choose three representative areas, the number of areas selected is left to the investigator's clinical judgment. The total number of raised and flat lesions (either total body or in the representative area(s)) must be counted.

NOTE: A representative area is a single extremity, the back, chest, or face that haslesions similar in characteristics (i.e., nodularity, size, color, and number, to those found on other parts of the body). A representative area does not need to be the area with the largest number of lesions but should contain lesions that are truly representative of those throughout the remainder of the body.

iii. Evaluate edema

Record the presence or absence of tumor-associated edema, the severity of edema,and the location of tumor-associated edema, if present. In addition, measure the circumference, in centimeters, of the ankle at the level of the malleoli and of the calf at a point 10 cm below the lower border of the patella. This must be done at **entry** in all participants whether there is edema or not.

iv. Perform oral examination

An oral mucosal tissue examination will be conducted on all study participants to detect the presence of oral cavity KS lesions.

The standardized oral mucosal tissue examination will be conducted wearing gloves and using 1 mouth mirror and 2 x 2 inch gauze. The oral examination shouldbe conducted in the following sequence:

Lips

Begin examination by observing the lips, with the mouth both closed and opened.Note the color, texture, and any surface abnormalities of the upper and lower lip.

Labial mucosa

With the mouth partially open, visually examine the lower labial mucosa by pullingthe lower lip and stretching it over the chin, holding it between your thumb and index finger and using both hands. Repeat the same steps for the examination of theupper labial mucosa by pulling the upper lip and stretching it over the nose.

Buccal mucosa and vestibules

With the mouth open wide, using the mouth mirror as retractor, examine first the right buccal mucosa (inside of cheek) extending from the labial commissures (corner of the lips) and back to the anterior tonsilar pillar. Examine both the upperand lower vestibule using the mirror to stretch the buccal mucosa and to help visualize the posterior vestibules. Examine the left buccal mucosa, following the same guidelines.

Hard and soft palate

With the mouth wide open and the participant's head tilted backwards, gently depress the base of the tongue with the mouth mirror. First, inspect the hard palate(note the ridges or rugae) located in the anterior part, and then the soft palate and uvula (ask the participant to say "ahhh" to better visualize the soft palate).

Tongue

With the participant's tongue at rest and mouth partially open, inspect the dorsum of the tongue for any swelling, ulceration, coating, or variation in size, color, or texture. Also note any change in the pattern of the papillae covering the surface ofthe tongue and examine the top and the tip of the tongue. The participant should then protrude the tongue, and the examiner should gasp the tip of the tongue with apiece of gauze to assist with full protrusion and allow examination of the margins or lateral borders. Note the small "lumps" located on each side of the posterior lateral tongue in the base of tongue area; these are the foliate papillae (considered to be an extension of the lingual tonsils). Then observe the ventral surface.

Floor of mouth

With the tongue still elevated, inspect the floor of the mouth for swellings or otherabnormalities.

Gingiva

First, examine the buccal and labial aspects of the gingiva and alveolar ridge. Startwith the right maxillary posterior gingiva and alveolar ridge and move around the arch to the left posterior gingiva. Continue with the left mandibular posterior gingiva and alveolar ridge and move around the arch to the right posterior gingiva.

Second, examine the palatal and lingual aspects as has been done on the facial side,from right to left on the palatal (maxilla) and left to right on the lingual (mandible).Use the mouth mirror to retract the posterior part of the tongue and focus the light to better visualize the lingual gingiva.

Record the presence or absence of oral cavity KS lesions and their location as required by the CRF. Record whether lesions are raised or flat.

v. Evaluating disease that cannot be measured (evaluable disease, visceral KS)

Evaluable disease (also known as non-measurable disease) is disease that cannot bemeasured directly by the size of the tumor but can be evaluated by other methods. For purposes of this study, lesions considered truly non-measurable include: ascites, pleural or pericardial effusions, lymphangitic lung disease, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, bone metastases without an identifiable soft tissue component that can be evaluated by cross-sectional imagingtechniques, and lesions that can be identified only by endoscopic, bronchoscopic, or laparoscopic techniques. Changes in the size of other types of disease may not be accurately quantifiable, for example discrete lung lesions measuring less than 2cm in greatest diameter on chest X-ray (CXR).

A CXR will be performed at screening. If the CXR findings are consistent with pulmonary KS and a non-KS cause of an abnormal CXR is not identified after appropriate evaluations, according to local standards of care, pulmonary KS will be presumed to be present.

At screening, potential study participants must be asked about the presence of gastrointestinal (GI) symptoms (nausea, vomiting, rectal bleeding, and/or abdominal pain). If GI symptoms are present, further evaluations with locally available methods (e.g., stool tests for occult blood, intestinal parasites, upper and/or lower GI endoscopy) should be undertaken as appropriate according to local standards and availability of diagnostic procedures. Treatable causes of GI symptoms (e.g., infections, peptic ulcers or acid reflux) will be treated per local standards of care. In the absence of direct visualization of pigmented lesion(s) consistent with KS on endoscopy (with or without biopsy confirmation), a presumptive diagnosis of GI KS cannot be made. However, participants with otherwise unexplained GI symptoms that might be indicative of GI KS will be followed during study treatment to determine if symptoms change during treatment.

KS involving other visceral organs can be detected by advanced imaging techniques(e.g., CT or MRI scan, ultrasound) and confirmed by biopsy. If KS is confirmed by biopsy in visceral organs, this information should be recorded. If there is an unconfirmed abnormality on a scan or ultrasound, and KS cannot be confirmed by biopsy, that information should be recorded and the abnormality followed during study treatment to determine if it changes.

For purposes of response assessment, the evaluation of non-measurable disease is used primarily to determine whether an individual has shown tumor progression when evaluation of measurable disease (i.e., cutaneous marker lesions, lesion counts, numbers of raised and flat lesions, edema, visceral disease that is measurable in two dimensions on CT scan) indicates response or stable

disease. We will use the standard of "unequivocal progression" (i.e., an *overall* level of substantial worsening of disease that is of a magnitude that) even in the presence of stable disease or partial response in measurable disease, the treating physician would feel it important to change therapy. This requires clinical judgment on the part of the investigator. For further guidance on the evaluation of non-measurable disease, please refer to the following:

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3): 205-216.

1.2 Kaposi Sarcoma Tumor Response Exam

The KS tumor response exam will be performed according to the schedule of events. Tumor evaluation should include:

- **Record** measurements of the longest linear dimension in millimeters and the longest dimension perpendicular to it of the same marker lesion**(s)** selected at entry;
- **Record the** total number of raised and flat lesions (in the same **areas that were evaluated at entry, either total body or the representative area(s)** selected at entry);
- **R**ecord the location, size, or characteristics of oral cavity lesions, after the oral mucosal tissue examination is conducted in the same sequence as the oral examination at entry;
- **R**ecord the severity of edema and the location of tumor-associated edema. If no edema was present at **entry** and no edema is present on the follow-up visit, repeat measurements are not required. If there was no edema at **entry** and edema develops at a subsequent visit, a re-measure at each subsequent KS evaluation is required. If edema was noted at **entry**, a re-measure at each subsequent KS evaluation is required.
- Record changes of visceral KS at the intervals required by the protocol if visceral disease was present at entry, or if symptoms suggesting visceral disease develop.

1.3 Calculating Response Status

Response status will be classified as complete response **(CR),** partial response **(PR)**, stable disease, or progressive disease (**PD**).

i. Calculate response status based on area of marker lesion(s)
   To calculate the KS response status **based on area of marker lesions** you will need the area of the indicator lesions from entry. Next, calculate the area of the same indicator lesion(s) for the current visit. Subtract the area at the current visit from the area at entry, and then divide this difference by the area at entry. **Multiplying by 100% will give you** the percentage change from entry. After a participant has had a **confirmed CR** or **PR**, subsequent measurements for PD should be compared with the "best response" seen at a previous visit.

   A**n initial confirmed PR** is a ≥ 50% decrease in the area of the indicator lesion(s)compared to entry **lasting for at least 4 weeks**. For example, if a participant had an area of the indicator lesions of 4000 mm² at entry and an area of the indicator lesions of 2000 mm² at week 4, and this decrease was maintained for at least 4 weeks, the participant would have a **confirmed PR**.

   PD is considered a ≥ 25% increase in the area of the indicator lesion(s) compared to entry or best response. For example, if the same participant as in the example above had an area of the indicator lesions of 5000 mm² at week 4, the participant would have PD. Similarly, if a participant had an area of the indicator lesions of 4000 mm² at entry and an area of the indicator lesions of 2000 mm² at week 12 **that lasted for four weeks** (a **confirmed PR**) but at a subsequent visit was found have an area of 3000 mm² (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmedCR.**

   NOTE: If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** area of the indicator lesions was 5000 mm²and the area decreased to 2400 mm² at week**s 4, 6 and 8**, this would be the initial **confirmed PR**. If, at week **12**, the area of the indicator lesions decreased further to2000 mm**², then 2000 mm² is the new "best response." In this example, subsequent assessments of PD for the area of indicator lesions would be with respect to the number 2000 mm², not to 2400 mm². Thus, if the area of the indicator lesions at week 12 increased from 2000 to 2500 mm², this increase would constitute PD, despite the fact that 2500 mm² is 50% smaller than the entry lesion area.**

NOTE: If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be reported as PR. In the example above, if the entry area of the indicator lesions was 5000 mm² and the area decreased to 2400 mm² at weeks 4, 6 and 8, and remained at 2400mm²at week 16, 2400 mm² is the "best response" to date. If, at week 24, the area of the indicator lesions increased to 2800 mm² this would continue to be reported as a PR because 2800 is less than a 25% increase from 2400. Similarly, if at week 24, the area of the indicator lesions decreased by an additional 10% to 2160 mm², this would also continue to be reported as aPR.

ii. Calculate response status based on the total number of lesions

To calculate the response status based on the total number of lesions, you will need the total number of lesions (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) from the entry KS exam. After an initial **confirmed CR** or **PR**, the percentage change for PD should be calculated from the "best response" seen at a previous visit.

An **initial confirmed PR** is a 50% or greater decrease in the number of lesions present at entry (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) **lasting for at least 4 weeks**.For example, if a participant had 40 lesions at entry and had only 20 lesions at subsequent tumor evaluation and this decrease was maintained for at least 4 weeks, that participant would have a **confirmed PR**.

For participants with ≤ 50 cutaneous lesions **at entry,** PD is defined as ≥ 25% increase in the total lesion count or a minimum of five new lesions**, whichever is greater,** compared to entry or best response. For example, if a participant had 35 lesions at entry and has 44 at subsequent evaluation that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

NOTE: If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.

For participants with > 50 cutaneous lesions **at entry,** PD is defined as ≥ 25% increase in the total number of lesions **or a minimum of five new lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions **compared to entry or best response,** or a total of five new lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease. For example, if a participant had a total of 40 lesions at entry on the back and the right leg and had a total of 50 lesions at subsequent visit on the back and the right leg that would be classified as PD. Also, if a participant had no lesions at entry on the right arm and had five lesions on the right arm at subsequent visit that would be classified as PD. Similarly, if a participant had 40 lesions at entry and 20 lesions at week**s 4, 6, and 8** (a **confirmed PR**) but at a subsequent visit was found to have 30 lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of lesions was 30 and the number of lesions decreased to 15 at week**s 4, 6 and 8**, this would be the initial **confirmed PR**. If, at the week 18 evaluation the number of lesions decreased further, e.g., to 10, **then 10 is the new "best response" and** subsequent assessments of PD for lesion counts would be with respect to the number 10, not to 15. **Furthermore, if the number of lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry lesion count.**

NOTE: If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, if the entry lesion count was 30 and the number of lesions decreased to 15 at weeks 4, 6, and 8, then 15 is the "best response" to date. If, at week 24, the number of lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, ifat week 24, the number of lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.

iii. Calculate response status based on the number of raised lesions

To calculate the response status based on the number of raised lesions, you will need the total number of raised **lesions** (either whole body or, in the case of participants with > 50 lesions at entry, in the combined representative areas) from the entry KS exam. If, after an initial **confirmed** response, the disease appears to be getting worse, the percentage change **for PD** should be calculated from the "best response" seen at a previous visit.

An **initial confirmed PR** is a complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesion become macules) present at entry (either whole body or, in the case of participants with > 50 lesions at entry, in the combined representative areas) **lasting for at least 4 weeks**. For example, if a participant had 30 raised lesions at entry and had only 15 raised lesions at subsequent evaluation and this decrease was maintained for at least 4 weeks that would be classified as a **confirmed PR**.

For participants with ≤ 50 cutaneous lesions **at entry**, PD is defined as ≥ 25% increase in the number of raised lesions (minimum of 5 new raised lesions if there are very few raised lesions, for example < 8), compared to entry or best response. For example, if a participant had 20 raised lesions at entry and had 25 raised lesions at subsequent evaluation that would be classified as PD. Also, if a participant had seven raised lesions at entry and had 12 at subsequent evaluation that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

NOTE: If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.

For participants with > 50 cutaneous lesions **at entry,** PD is defined as ≥ 25% increase in the total number of raised lesions **or a minimum of five new raised lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions (minimum of 5 raised lesions if there are very few raised lesions, for example < 8). For example, if a participant had a total of 28raised lesions on the back and right arm at entry and had a total of 35 raised lesions on the back and right arm at subsequent evaluation that would be classified as PD. Also, if a participant had a total of seven raised lesions on the back and right arm at entry and had 12 raised lesions on the back and right arm at subsequent evaluation that would be classified as PD. Similarly, if a participant had 40 raised lesions at entry and 20 raised lesions at week**s** 4, 6 **and 8** (a **confirmed PR)** but at a subsequent visit was found have 30 raised lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of raised lesions was 30 and the number of raised lesions decreased to 15 at week**s 4, 6, and 8**, this would be the initial **confirmed PR**. If, at the week 18 evaluation, the number of raised lesions decreased further (e.g., to 10) **then 10 is the new "best response" and** subsequent assessments of PD for raised lesions would be with respect to the number 10, **not to 15**. **Furthermore, if the number of raised lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry raised lesion count.**

NOTE: If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, it the entry raised lesion count was 30 and the number of raised lesions decreased to 15 at weeks 4, 6 and 8, then 15 is the "best response" to date. If, at week 24, the number of raised lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, if at week 24, the number of raised lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.

iv. Determining response status combining measurements of lesion size, character, and number and visceral disease and edema

Participants who show the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks, will be classified as having CR. In some individuals, residual skin color changes may remain visible at one or more sites of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered **PR**. In participants in whom all detectablecutaneous disease has resolved and in whom there are no visible pigmented maculesas described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

Participants who do not meet the criteria for **CR**, **PR**, or **PD** will be classified as Stable.

The criteria for classifying participants as showing either **PR** or **PD** are shown in the table**s** below.

Partial response

PR requires at least one of the highlighted criteria in the table below AND all of the categories shown on the same row, when compared to entry.

NOTE: If any of the criteria for PD have been met, even in the presence of a criterion for **PR**, it is considered PD.

NOTE: **PR** is always a comparison to entry even if there has been a prior **PR**.

*Please note that there is no need to physically measure the visceral or oral KS.

Criteria for Classifying **PR**					
Total Body or Representative Areas					
PR Category	Marker lesion	Number of lesions	Number of raised lesions	Visceral or Oral KS*	Edema
1	Decrease ≥ 50%	< 25% Increase	< 25% Increase	< 25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
2	< 25% Increase	Decrease ≥ 50%	< 25% Increase	< 25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
3	< 25% Increase	< 25% Increase	Decrease ≥50%	< 25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
4	< 25% Increase	< 25% Increase	< 25% Increase	Decrease ≥ 50% of measurable lesions without unequivocal worsening of non-measurable disease **or complete disappearance of non-measurable disease**	No significant increase or new sites

Progressive disease

Any of the following (increase refers to a change over entry visit or when compared to the best response). If there has been a previous **confirmed CR** or **PR**, subsequent assessments of PD should be made with comparison to the best response for the category (or categories) that previously led to the assessment of CR or PR; for the other categories, the comparison should be made to entry.

NOTE: PD is a comparison to entry unless there has been a **confirmed** PR or CR in which case it is then a comparison to best response. Only PD is compared to best response.

Total Body or Representative Areas				
Marker lesion area	Number of lesions	Number of raised lesions	Visceral or Oral KS	Edema
≥ 25% Increase	≥ 25% Increase	≥ 25% Increase	≥ 25% Increase or new sites or unequivocal worsening of non-measurable	Significant increase or new sites*

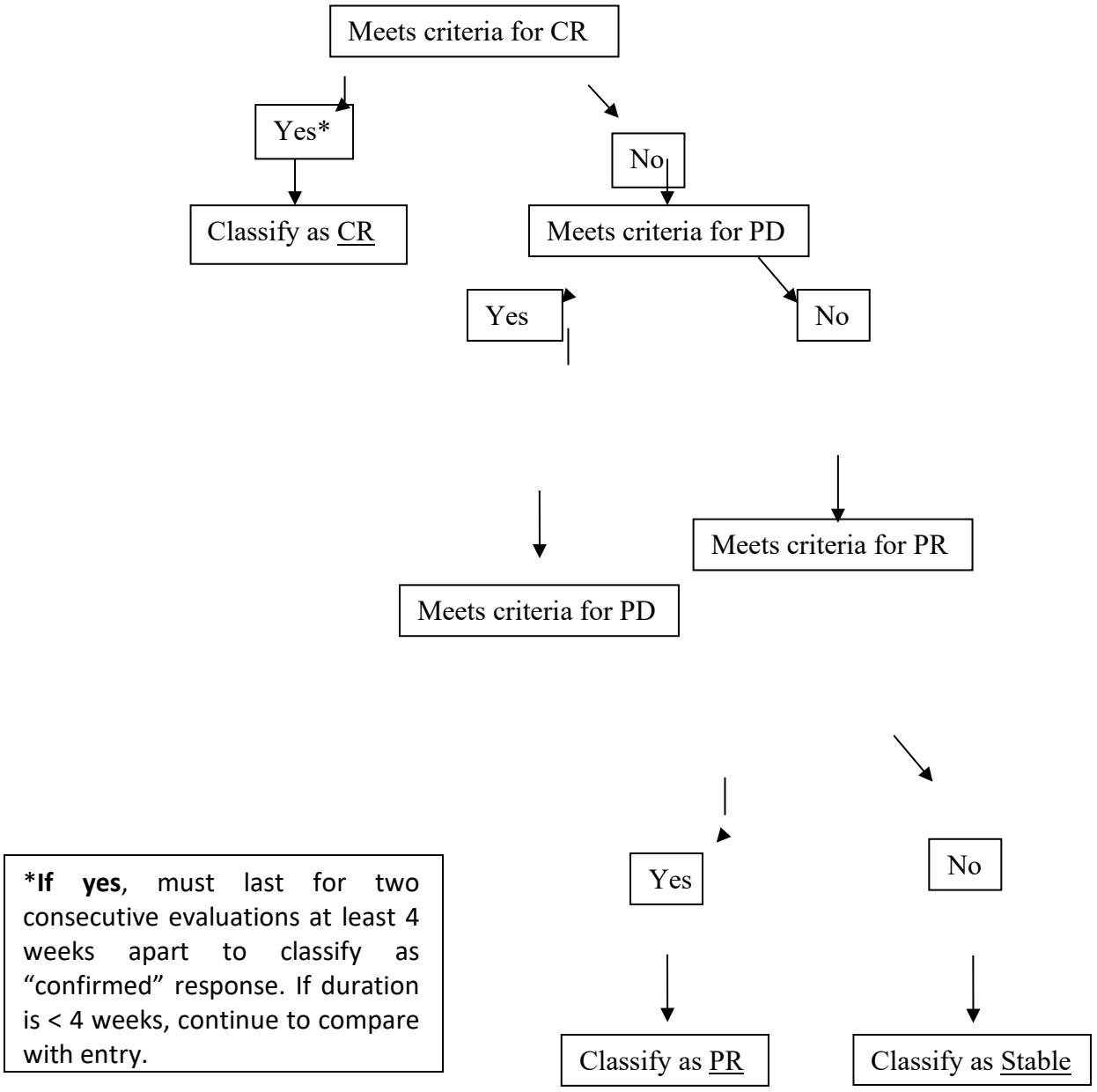
*Significant increase in edema **or new sites compared to entry or best response**** are defined as:

- An increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry **or best response**, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR,
- New appearance of non-pitting/woody edema in an extremity when none was previously present, sustained for at least two consecutive evaluations; AND/OR,
- New or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

** If edema is present at entry and resolves completely (and this lasts for at least 4 weeks), this is considered a "best response" of edema. Otherwise, all evaluations of edema in a given step are with respect to the status at entry to that step.

b. KS Response Assessment: Algorithms

1.4.1 Participant without prior confirmed **CR** or **PR**



***If yes**, must last for two consecutive evaluations at least 4 weeks apart to classify as "confirmed" response. If duration is < 4 weeks, continue to compare with entry.

1.4.2 Participants with prior confirmed CR

Once a CR is confirmed (i.e., it has persisted for 4 weeks or more), only two options are available for subsequent response classification: CR or PD (i.e., PR or Stable **D**isease are no longer response options).

A confirmed CR is, by definition, the "best response," so the appearance of <u>any</u> KS lesions after a confirmed CR must be classified as PD.

1.4.3 Participant with prior confirmed PR

Once a PR is confirmed (i.e., it has persisted for 4 weeks or more), only three options are available for subsequent response classification: CR, PR, or PD (i.e., Stable Disease is no longer a response option).

- If all residual KS disappears, and this persists for 4 weeks or more, then the patient has achieved a CR, and this is the "best response."
- A PR may improve with time.

Once a PR is confirmed, the "best response" up until that time is used as the basis for determining whether PD has occurred.

"Best Response" may be achieved in different categories (e.g., # of raised lesions,

# of total lesions, marker lesion area) at different times. Whichever is the best response in a given category would determine what to compare that category with on subsequent evaluations. For example, if "best response" for flattening of raised lesions is at week 16 and "best response" for total lesions is at week 24, then those timepoints should be used to compare raised lesions and total lesions, respectively, at later timepoints. PD in ANY category with respect to "best response" means that the Overall Response is PD.

2.0 PHOTOGRAPHIC RECORD

Photographs will be taken to assist in documentation of the diagnosis of KS and for clinical monitoring purposes. The difficulty in standardizing these photographs is acknowledged. Unless the AMC protocol defines a different schedule, lesion photographs will be collected at baseline, at the time of initial and maximal response, and at the final participant visit (off study).

In all participants, photographs will be needed of the marker lesion**(s)**, defined at study enrollment and used for clinical assessment of response. The marker lesion**(s)** must be labeled in the photographs #1 – #5, **as applicable**. The same lesion**(s)** must be consistently labeled throughout the trial. For each lesion, two photos will be taken. The first photo will be a close-up of the lesion. A millimeter ruler should be included in the photograph to demonstrate the size of the lesion. The second photo will be a larger view photo that will show the lesion's location on the body.

All participants will also need photos of larger views of the back, chest, arms (front and back), legs (front and back), feet (including soles), whether involved with KS or not. In addition, photos should be taken of any other area with significant involvement at baseline (e.g., the face).

In participants with > 50 cutaneous lesions, photographs will be taken of the representative areas (each **should have at least five** lesions), defined at study enrollment and used for clinical assessment of response.

Photographs will be stored electronically under the participant ID number and back-up electronic storage will be kept. Only dedicated study staff and the sponsor should have access to the photographs.

Appropriate measures must be taken to protect participant confidentiality. Photographs of participants' faces should be avoided unless the area is being monitored for KS response. In cases where a participant's face is photographed, no participant photos should be used in publication prior to removal of identifying characteristics, for example, the blacking out of a participant's eyes. **Site should take necessary measures to obscure eyes and/or tattoos.**

Absolutely no identifying information should be included with the digital picture file.

2.1 Photography Tips

1. We recommend a 5-megapixel camera minimum.
2. Include the participant ID number in all of the photos.
3. Always try to take the photos in the same setting with respect to participant positioning, lighting, background, and camera setting.
4. Use auto-focus. The team does not recommend the use of manual controls.
5. Use the "macro" mode for close-ups. The universal symbol for "macro" mode is a flower.
6. Use the flash mode as often as possible when the lighting is poor, but avoid getting too close to the lesions as overexposure may wipe out the details.
7. For very close shots, oblique views may be preferred.
8. Eliminate all distractions from the background. Try to take all photographs with a plain blue or green background.

2.2 Framing Tips

1. For different body areas certain standard framing patterns are followed
2. For all lesions, make it a point to take at least two shots from each point of focus. Minimal blurring may not be obvious on the LCD screen and may be noticeable only after the image is viewed on the monitor. It is always better to have an extra copy from every focus point so that the best image can be selected.
3. Always try to capture distinctive elements like typical representative lesions, particular configurations, or distribution patterns.

For generalized lesions take shots from at least three ranges:

- A complete vertical view of the participant showing the extent and distribution of the rash;
- A medium distance shot showing the arrangement and configuration of the rash;
- A close-up view highlighting a representative lesion.

For localized lesions take shots from at least two points:

- A medium view showing the rash /lesion with respect to location and configuration. Always include a recognizable body landmark so that the location is obvious. For example, lesions on the abdomen include the umbilicus in the medium distance shot)
- A close-up view of the representative lesion.
  For isolated lesions it is also advisable to include a discernible landmark in one of the shots. For the close-up shots use a measuring tape/ruler in the frame to demonstrate the size of the lesion. It would be advisable to take the close-up shots from more than one angle and include oblique shots. Shots with and without flash may be taken and the best shot selected for storage.

2.3 Saving and Storing Photographs

1. SAVE as a JPG file. The major advantage of the JPG format is that the image size can be compressed considerably without significant visible loss of resolution. The back- up copies can also be saved in the compressed JPG format so that the space taken up can be minimized. It always makes sense to delete images that are blurred as they are unlikely to be used by you and will unnecessarily clutter up the hard disk space.
2. Make it a point to catalog all saved images (or containing folders) tagging them with the participant's identification number, date and even the provisional diagnosis, if possible. Meticulous cataloging may seem cumbersome at the beginning but makes future retrieval of images very convenient.

2.4 Uploading Photographs to AdvantageEDC

All photographs required by this protocol and/or MOP will be uploaded to the KS response evaluation forms in AdvantageEDC/Advantage eClinical, as used for trial data entry. Refer to the AMC Advantage EDC or Advantage eClinical Forms Instructions for detailed instructions for photograph upload.