Cabozantinib and Pembrolizumab as a Front-line Therapy for Advanced Metastatic Melanoma

Protocol Number: Exelixis IST 59

National Clinical Trial (NCT) Identified Number: NCT03957551

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by Exelixis and the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form
DCC	Data Coordinating Center
DCR	Disease Control Rate
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
MTD	Maximum Tolerated Dose
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PR	Partial Response
QA	Quality Assurance
QC	Quality Control
ORR	Overall Response Rate
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States

1. PROTOCOL SUMMARY

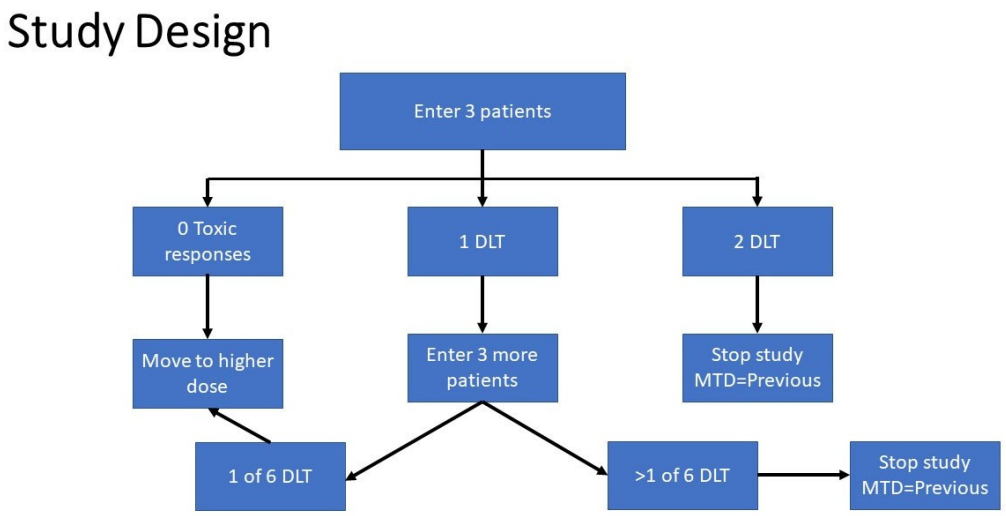
1.1 SYNOPSIS

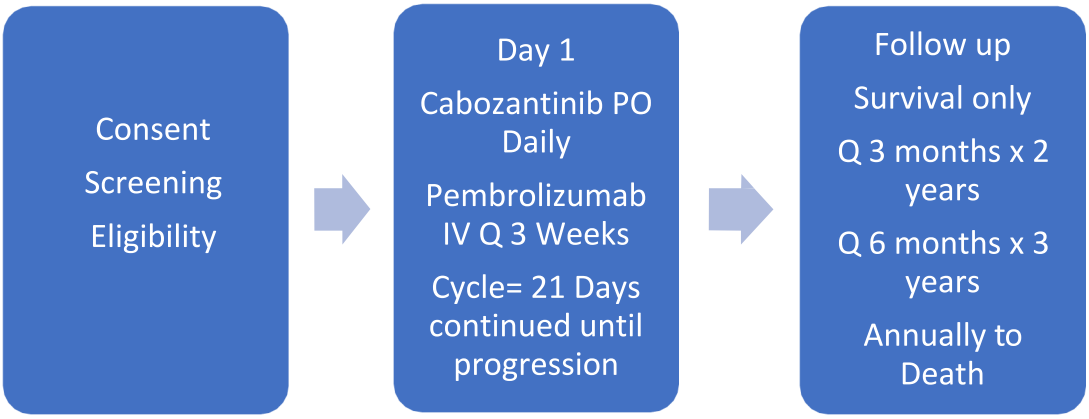
Title:	**A Phase 1b/ 2 Study of Cabozantinib in Combination with Pembrolizumab in Advanced Melanoma**
Study Description:	The study aims to evaluate the safety and preliminary efficacy of the combination of cabozantinib and pembrolizumab in advanced melanoma. The phase 1b study is based on 3+3 design with fixed dose of pembrolizumab and three dose levels of cabozantinib. The phase 2 study will be conducted in two stages, with a hypothesis of improving the response rate to 55%.
Objectives:	Phase 1b: To establish the recommended phase 2 dose of cabozantinib in combination with pembrolizumab in patients with unresectable melanoma and assess the safety and tolerability of the combined treatments. Phase 2: To evaluate the preliminary efficacy of the established dose of cabozantinib in combination with pembrolizumab as measured by best overall response rate (ORR) (complete response (CR) + partial response (PR)) with the combination of agents in patients with unresectable stage III or stage IV melanoma.
Endpoints:	Phase 1b: Combination of cabozantinib and pembrolizumab is safe to use in advanced melanoma Primary Endpoint: Objective response rate Secondary Endpoints: Clinical benefit (DCR and duration of DCR), time to response, progression-free survival and overall survival.
Study Population:	Adults with unresectable stage III or stage IV advanced melanoma
Phase:	1b/2
Description of Sites/Facilities Enrolling Participants:	This single center study will be conducted at the Holden Comprehensive Cancer Center of the University of Iowa Hospitals and Clinics. The biomarker part of the study will be decided at a later date.
Description of Study Intervention:	A combination of cabozantinib and pembrolizumab will be tested in the study. Cabozantinib will be administered in the tablet form, at three dose levels: 40, 20 and 60 mg per day. Pembrolizumab will be administered as an intravenous infusion at a fixed dose of 200 mg once every 3 weeks.

1.2 SCHEMA

Phase 1b:

Dose Level	Cabozantinib	Pembrolizumab
-1	20 mg	200 mg
0	40 mg	200 mg
1	60 mg	200 mg





Phase 2: The target population includes patients with pathologic or cytologic evidence of melanoma, clinical stage IV or recurrent/medically inoperable disease, a ECOG performance score ≤ 2and a life expectancy of >12 weeks, adequate hematologic, renal, and hepatic function, and measurable disease.

Patients who are taking other investigational agents, or who have uncontrolled CNS metastases or unstable medical conditions such as decompensated heart failure, unstable angina, uncontrolled hypertension or diabetes and active infections are to be excluded from this study. Treatment will begin only after patients have fully met all inclusion criteria and none of the exclusion criteria and a valid informed consent has been signed.

Subjects will receive cabozantinib, orally at the MTD dose obtained from phase 1b part of the study in combination with pembrolizumab administered IV at 200 mg once every 3 weeks. After baseline tumor evaluation, tumor assessments will be performed with interval imaging every 12weeks starting from Week 12 until progression with a CT scan and response evaluated per RECIST 1.1. Appendix A. Progressive disease per RECIST or unacceptable toxicity will result in the subject's termination of the study drug.

Prognostic Stage Group: the eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system groups patients into four prognostic stage groups. The details of prognostic group staging:

- Stage I – Stage I melanoma is limited to patients with low-risk primary melanomas (T1a, T1b, and T2a) without evidence of regional or distant metastases. Stage I is divided into stages IA and IB based upon the thickness of the primary tumor and the presence or absence of ulceration.

- Stage II – Stage II disease includes primary tumors that are at higher risk of recurrence (T2b, T3a, T3b, T4a, and T4b) but do not have any evidence of lymphatic disease or distant metastases. Stage II is divided into stage IIA, IIB, and IIC depending upon tumor thickness and the presence or absence of ulceration.

- Stage III – Stage III disease includes pathologically documented involvement of regional lymph nodes or the presence of in transit or satellite metastases (N1, N2, and N3). Patients with stage III disease are subclassified as having stage IIIA, IIIB, IIIC, or IIID disease depending upon the extent of lymphatic disease.

    - Unknown primary – Patients with isolated metastases identified in the lymph nodes, skin, or subcutaneous tissue who do not have an identifiable primary cutaneous melanoma (T0) are classified as pathologic stage III, assuming no other sites of disease are identified after an appropriate staging evaluation. Other sites of metastases from an unknown primary melanoma are classified as stage IV.

- Stage IV – the presence of distant metastases defines stage IV disease (M1a to M1d). Central nervous system metastases (M1d) are associated with a particularly poor prognosis. There are no subgroups.

1.3 STUDY CALENDAR

Assessments	Screening 28-day window up to Day 1 of treatment[1]	Day 1 of Every ODD Cycles (1, 3, 5…) +/- 5 days	Day 1 of every EVEN cycle Cycles (2, 4, 6…) +/- 5 days	END of Treatment Visit[2]	Follow Up[3] (every 3M from EOT Visit
Informed Consent[4]	X				
Inclusion/Exclusion Criteria	X				
Medical History/ Prior Treatment[5]	X				
Concomitant medications	X	X	X	X	
Physical Exam	X	X	X	X	
Performance Status (ECOG or KPS)	X	X	X	X	
Vital signs/Weight/Height[6]	X	X	X	X	
Drug Toxicity Assessment[7]	X	X	X	X	
Baseline daily stool count	X				
ECG [8]	X[9]	EVERY 12 weeks (Pre-Cycle 5, 9, 13, …)		X	
ECHO- 2D/MUGA	X				
Pregnancy test[10]	X				
CBC with Differential[11]	X	X	X	X	
Chemistries[12]	X	X	X	X	
PT/INR and PTT[13]	X			X	
Urinalysis and UPC	X	X	X	X	
Thyroid Function Tests[14]	X		X	X	
Amylase, Lipase	X	Every 12 weeks (Pre-Cycle 5, 9, 13…)		X	
Hepatitis B and C [15]	X				
Tumor Imaging- CT Chest/Abdomen/Pelvis[16]	X	Every 12 weeks (Pre-Cycle 5, 9, 13…)		X	
Brain MRI[17]	X				
Pill Diary/Pill Count[18]		X	X	X	
Research Blood[19] Phase II only	X	At week 7 (+/- 1 week) and progression			
Archival Tissue[20] Phase II only	X				
Tissue Biopsy[21] Phase II Part 2 only	X	At week 7 (+/- 1 week) and progression			
Cabozantinib PO		Daily	Daily		
Pembrolizumab IV (30-minute infusion)		Day 1 of each Cycle			
Survival Status					X

[1] Routine laboratory tests for screening should be performed within 14 days of cycle 1.
[2] End of treatment visit will be completed 30 days (+/- 7 days) from date of last dose of study drug or before another treatment starts whichever occurs first.
[3] Subjects will be followed for survival and progression post treatment every 3 months x 2 years, every 6 months x 3 years and yearly until death. Every 3 months from EOT visit.
[4] Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in –lieu of a screening test if performed within the specified time frame. (e.g., within 28 days period to Cycle 1 Day 1.)
[5] Report complete medication history for 30 days prior to the screening visit. Medical history should include history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment and best response to prior systemic treatments. Date of last prior cancer treatment must be documented.
[6] Vital signs to include weight, temperature, pulse, respiratory rate and blood pressure. Height will be measured at screening only.
[7] Adverse events and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All adverse events, whether gradable by CTCAE or not, will also be evaluated for seriousness.
[8] ECG must be completed within 14 days before Cycle 1 Day 1. If at any time on study, there is an increase in QTcF interval to an absolute value > 500 ms, two additional ECGs must be performed, within 30 minutes after the initial ECG (each with intervals 2 minutes apart).
[9] Triplicate ECGs will be performed at screening only with intervals of at least 2 minutes apart. Single ECGs will be done every 12 weeks and at EOT.
[10] For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose of therapy. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy test (serum and/or urine) should be repeated if clinically indicated.
[11] Routine laboratory tests may be collected up to 48 hours prior to Day 1 of any Cycle.
[12] Chemistries to include: Glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST, LDH, GGT, phosphorus and magnesium.
[13] PT/INR and PTT will be collected at Screening, End of Treatment and as clinically indicated.
[14] T3, Free T4, and TSH will be performed at screening, Day 1 of EVEN Cycles and EOT visit.
[15] Subjects will be tested for hepatitis B and C during screening if they are considered by the investigator to be at higher risk for these infections and have not been previously tested.
[16] Tumor imaging will be performed within 28 days prior to enrollments. CT Chest/Abdomen/Pelvis with contrast is required unless a patient has a clinical condition such as a severe contrast allergy or the lesions are significantly better visualized through the use of an MRI. The same imaging technique must be used in a subject throughout the study. In addition, subjects with progressive disease consider a second scan in at least 4 weeks to confirm progression and exclude the possibility of a tumor flare reaction, according to irRC guidelines, this would be at the investigator discretion. If there is an increase in tumor burden at week 12, the baseline sum of perpendicular diameters is to be reset to week 12 for subsequent assessment of response.
[17] If clinically indicated.
[18] Subjects should use a study pill diary (Appendix C) to record their daily dose of cabozantinib. Subjects should bring the pill diary with them each time they return for a study visit. Study pill counts will be done at the end of each cycle prior to dispensing a new supply of study medication. Reasons for discrepancies in pill counts will be documented in the subject's study binder.
[19] Phase II only: 5 tubes of blood will be drawn at baseline, week 7(+/- 1 week) and at progression for future biomarker testing.
[20] Phase II only: An archival tissue sample of at least one tumor lesion is mandatory. If archival tissue is not available subject must agree to a new biopsy sample.
[21] Phase II Part 2 only: An optional tumor tissue core biopsy will be performed at 7weeks (+/- 1 week) and at time of progression. Recommend: Per PI discretion, Cabozantinib be held for 4 days prior to biopsy and restarted 7 days after biopsy provided adequate wound healing is achieved.

2 INTRODUCTION

2.1 STUDY RATIONALE

An estimated 76,380 adults (46,870 men and 29,510 women) in the United States were diagnosed with melanoma of the skin in 2016[1] with estimated 10,130 deaths (6,750 men and 3,380 women). The estimated 5-year survival for patients with unresectable/metastatic melanoma is 17%. In the United States, melanoma is the fifth leading cancer in men and the seventh in women. An estimated 73,800 individuals will be diagnosed with melanoma and 9,900 will die of the disease in 2015 in the Unites States despite current therapy.

Over the last few years several new drugs including the immuno-oncology agents ipilimumab[1], nivolumab[2], and pembrolizumab[3]as well as inhibitors of protein kinases BRAF and mitogen-activated protein kinase (MAPK)/ERK kinase (MEK) have been approved for use in patients with activating mutations in *BRAF*[4-7]. Although these agents have extended survival in treated populations, and induced durable responses, the response rates are in the range of 35-40%.

Combination treatment approach has been explored in the management of advanced melanoma. A combination of ipilimumab and nivolumab improved the overall response rate and progression free survival [8], however toxicities are much more frequent and severe, with AEs of any grade observed in almost every patient and grade 3 to 5 AEs in 55% to 60%, with 40% of patients interrupting treatment for toxicity [9](Boutros Nat rev clin onc, 2016). Therefore, newer and safer combination treatment options are needed for the management of patients with advanced melanoma.

2.2 BACKGROUND

2.2.1 PRECLINICAL EVIDENCE

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure). The primary targets of XL184 are MET (c MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, TYRO3, MER 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[10]. Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers. The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF)[10] (Christensen, J.G. et al c-MET as a target for human cancer) c- Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three- dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies

including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's brochure). c-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

The receptor tyrosine kinase MET and its cognate ligand hepatocyte growth factor (HGF) has been implicated in diverse aspects of tumor pathobiology, including tumor growth, survival, neoangiogenesis, invasion, and dissemination[11] MET pathway activation and dysregulation have been implicated in multiple cancers, including melanoma. In a survey of 40 malignant melanoma specimens, MET expression and activation was evident in 88% and 21% of cases, respectively [12]. In a genomic survey, the gene encoding MET was amplified and overexpressed in metastatic melanomas compared with primary melanomas[13]. MET activation, which may be driven by stromal HGF expression, has been shown to mediate melanoma growth, dissemination, and resistance to BRAF inhibition in multiple preclinical models[12-15]. AXL also regulates melanoma growth and migration and has been implicated in resistance to BRAF inhibition [16-18]. VEGFR kinase inhibitors and anti-VEGF antibodies are part of standard therapy for numerous solid tumor malignancies and have been explored in melanoma[19].

Immunomodulation: TYRO3, AXL, and MER (TAM) receptor tyrosine kinases are immune inhibitor receptors, which may serve as relevant targets for innate checkpoint blockade. AXL and MER participate in defending the host from pathogens by preventing attack on the host or "self" cells, which involves preventing an overactive inflammatory response. Maintaining the balance of AXL and MER expression, which is regulated by different pathways to control the inflammatory response, is complex, and their normal roles in terminating innate immune-mediated inflammation and natural killer cell responses are suppressed in the tumor microenvironment. TAM RTKs are involved in suppressing innate immune cells by modulating the activity of antigen presenting cells such as dendritic cells (DC), which can permit tumor cell migration[21]. VEGF also has a significant role in immune response of by inhibiting DC maturation[22]. VEGFR- targeted therapy was also found to alleviate the immunosuppressive tumor microenvironment by normalizing vascularization and reduced the myeloid-derived suppressor cells (MDSC; CD11b+, Gr+) with immunosuppressive activity[23].

Immuno-modulatory effects of cabozantinib have been described in vitro and in murine models for several cancers including RCC, colorectal cancer (CRC), and prostate cancer. Moreover, cabozantinib appears to exert its effect on regulatory T cells (Tregs) via the HGF/c-Met pathway, where this receptor signaling cascade mediates multiple immune cell functions[24]. HGF was shown to suppress DC function and in turn induce Tregs (CD4+ CD25+ FoxP3) in a murine central nervous system (CNS) autoimmunity model[25]. HGF cultured monocytes differentiate into monocytic cells that produce soluble factors (e.g., IL-10) that favor immune suppressive conditions ideal for tumor development[26]. The activation of the HGF/c-MET signaling cascade activates the Ras/Raf signaling pathway and prevents apoptosis of renal cancer cells as well as facilitates escape of tumor cells from immune cell mediated killing[27]. In co-culture of programmed death receptor 1 (PD-1) expressing murine splenocytes and programmed death receptor 1 ligand (PD-L1)

overexpressing renal cancer cells, an increase in apoptosis occurred in the presence of a c-Met inhibitor or PD-L1 neutralizing antibody. The activation of Ras by c-Met leads to induction of hemeoxygenase-1 (HO-1). HO-1, a cytoprotective molecule released during oxidative stress, can modulate the tumor microenvironment and promote cell proliferation and invasiveness in a number of cancers[28]. Balan et al showed that c-Met also induces PD-L1 overexpression, which is associated with a reduction in splenocyte-mediated apoptosis of renal cancer cells[29]. In human renal cancer tissues that were examined in the study, both c-Met and PD-L1 were found to be co-localized and overexpressed. Collectively, these results suggest a mechanism for renal tumor cell escape from immune cell mediated killing and apoptosis.

For example, prostate cancer (Ptenfl/flTrp53fl/fl) mice, age between 5 to 6 months, with aggressive prostate cancer were treated with cabozantinib[30]. Cabozantinib-treated mice showed an approximately 70% reduction in tumor volume, which was accompanied by decreased FDG-PET signal, histopathology revealed a near-complete clearance of the poorly differentiated, invasive prostate carcinoma in 4 days, which was sustained over 3 weeks of cabozantinib treatment. This was accompanied by increased perivascular ICAM1 staining and hypersegmented, Ly6G+, myeloperoxidase+ (MPO+) neutrophil infiltration into the tumor within 24 to 48 hours of treatment. Flow cytometry also showed an increase in CD11b+GR1+ tumor-infiltrating immune cells following 72 hours of cabozantinib treatment. qPCR-based RNA profiling of cabozantinib-treated tumors revealed a spike in gene expression of the chemokine CXCL12 and its receptor CXCR4 within the tumor microenvironment following 24 hours of cabozantinib treatment. An increase in intratumoral CXCL12 staining by RISH following cabozantinib treatment specifically in PTEN-deficient cells within the microenvironment, suggesting that the increase in CXCL12 expression was predominantly occurring in the tumor cells. Further characterization of the acute immunologic response in PTEN/p53-deficient prostate tumors from mice treated with cabozantinib revealed an increase in intratumoral CD86 expression by IHC and qRT-PCR and an increase in CD11b+, CD86+ cells by flow cytometry, demonstrating maturation and activation of myeloid antigen-presenting cells. Taken together, these data confirm the critical role of cabozantinib-mediated HMGB1 release from tumor cells, resulting in enhanced neutrophil chemotaxis and activation. This reprogramming of the tumor inflammatory/immune chemokine network within the tumor microenvironment triggers a robust neutrophil infiltration and invasive cancer eradication[30].

2.2.2 CLINICAL EVIDENCE:

2.2.2.1 PHASE I STUDIES:

Study XL184-001 was a phase 1 dose-escalation study in subjects with solid tumors[31,32]. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) 175mg and 265mg qd (using PIB), and 175 mg and 250 mg qd (using capsules [25 and/or 100mg]) were enrolled. The capsule MTD was determined to be 175 mg qd (Kurzrock Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer). Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%)

had tumor shrinkage of ≥ 30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects[31].

2.2.2.2 PHASE 2 STUDIES:

Study XL184-203 was a phase 2 randomized discontinuation trial[36]. Subjects were enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors received open label cabozantinib at starting dose of 100 mg qd for 12 weeks. A total of 526 patients were enrolled. The highest ORR was observed in ovarian cancer (OC) (21.7%); the largest PFS benefit was observed in castration-resistant prostate cancer (CRPC) (median 5.5 versus 1.4 months for placebo; hazard ratio 0.14, 95% confidence interval: 0.04, 0.52). Disease control rates were >40% for CRPC, OC, melanoma, metastatic breast cancer (MBC), hepatocellular carcinoma (HCC) and non-small cell lung cancer. Median duration of response ranged from 3.3 (MBC) to 11.2 months (OC). Dose reductions to manage adverse events (AEs) occurred in 48.7% of patients. The most frequent grade III-IV AEs were fatigue (12.4%), diarrhea (10.5%), hypertension (10.5%) and palmar-plantar erythrodysesthesia syndrome (8.7%).

A phase 2 randomized discontinuation trial was conducted to test the activity of cabozantinib (100 mg daily) in advanced melanoma. Among the 54 patients with available mutation data, *BRAF* mutations were detected in 31%. Sixty-six per cent of patients had at least one line of prior systemic therapy. Seventy-seven patients were enrolled and at week 12, 26 patients (34%) were randomized to receive either cabozantinib or placebo, and 10 patients (13%) continued open-label treatment with cabozantinib. Five of these 10 patients had experienced a partial response (PR); 4 of these were later determined to be confirmed PRs. The remaining five patients had SD at week 12 based on the final data analysis. The overall response rate was 5%; 39% of patients had SD. Median progression-free survival from study day 1 was 3.8 months, 6-month progression-free survival was 33%, and median overall survival was 9.4 months. This initial single agent study shows promising clinical activity.

A phase 2 study of XL 184 in renal cell carcinoma in combination with sunitinib was recently reported. This randomized Phase 2 trial enrolled subjects with untreated clear cell locally advanced or metastatic RCC and was designed to evaluate whether cabozantinib increased PFS compared with sunitinib, the most frequently used first-line RCC therapy. This study was sponsored by CTEP and conducted by The Alliance for Clinical Trials in Oncology (Alliance) and results were reported in the Journal of Clinical Oncology (Choueiri et al 2017). Eligible subjects had ECOG performance status of 0 to 2 and were intermediate- or poor-risk per the International Metastatic Renal Cell Carcinoma Database Consortium criteria. A total of 157 subjects were randomly assigned to either the cabozantinib arm (n = 79) or the sunitinib arm (n = 78). Subjects in the cabozantinib arm were treated with 60 mg cabozantinib qd, and subjects in the sunitinib arm were treated with 50 mg sunitinib qd for 4 weeks followed by a 2-week rest per 6-week cycle.

The analysis of the primary endpoint of PFS was reported by the Alliance after 123 events

had occurred (with 123 events, the log-rank statistic had 85% power to detect an HR of 0.67, assuming a one-sided type 1 error of 0.12). The HR adjusted for stratification factors was 0.66 (95% CI: 0.46, 0.95). Median PFS was 8.2 months (95% CI: 6.2, 8.8) in the cabozantinib arm and 5.6 months (95% CI: 3.4, 8.1) in the sunitinib arm [39].

The safety population consisted of 78 subjects treated with cabozantinib and 72 subjects treated with sunitinib. The incidence of Grade 3 or 4 AEs regardless of causality was 67% in the cabozantinib arm and 68% in the sunitinib arm. The most frequent Grade 3 or 4 AEs in the cabozantinib arm were hypertension (28%), diarrhea (10%), PPES (8%), and fatigue (6%). Grade 5 AEs regardless of causality occurred in 4 subjects (5%) in the cabozantinib arm and 5 subjects (7%) in the sunitinib arm. Treatment-related Grade 5 AEs occurred in 3 subjects in the cabozantinib arm (acute kidney injury, jejunal perforation, and sepsis) and 3 subjects in the sunitinib arm (respiratory failure, sepsis, and vascular disorders).

2.2.2.3 PHASE 3 STUDIES

The XL 184-308 (METEOR) study enrolled 375 patients with renal cell carcinoma who were randomized 1:1 to receive either cabozantinib (60 mg, tablet formulation) or everolimus (10 mg) which was a standard of care for the second line setting at the time of the initiation of the study[40].). The median duration of follow-up for overall survival and safety was 18·7 months (IQR 16·1–21·1) in the cabozantinib group and 18·8 months (16·0–21·2) in the everolimus group. Median overall survival was 21·4 months (95% CI 18·7–not estimable) with cabozantinib and 16·5 months (14·7–18·8) with everolimus (hazard ratio [HR] 0·66 [95% CI 0·53–0·83]; p=0·00026). Cabozantinib treatment also resulted in improved progression-free survival (HR 0·51 [95% CI 0·41–0·62]; p<0·0001) and objective response (17% [13–22] with cabozantinib *vs* 3% [2–6] with everolimus; p<0·0001) per independent radiology review among all randomized patients. The most common grade 3 or 4 adverse events were hypertension (49 [15%] in the cabozantinib group vs 12 [4%] in the everolimus group), diarrhea (43 [13%] vs 7 [2%]), fatigue (36 [11%] vs 24 [7%]), palmar-plantar erythrodysaesthesia syndrome (27 [8%] vs 3 [1%]), anemia (19 [6%] vs 53 [17%]), hyperglycemia (3 [1%] vs 16 [5%]), and hypomagnesemia (16 [5%] vs none). Serious adverse events grade 3 or worse occurred in 130 (39%) patients in the cabozantinib group and in 129 (40%) in the everolimus group.

Study XL184-301 was a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo[37]. SAEs reported in Study XL184-301 were: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5). The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR 0.28; 95% CI, 0.19 to 0.40; p < .001)[41]. Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and RET mutation status (hereditary or sporadic). Kaplan-Meier estimates of subjects alive and progression-free at 1 year were 47.3% for cabozantinib and 7.2% forplacebo."

Kaplan-Meier analysis showed a 5.5-month increase in median OS with cabozantinib versus

placebo (26.6 versus 21.1 months) although the difference did not reach statistical significance [stratified hazard ratio (HR), 0.85; 95% confidence interval (CI), 0.64-1.12; P = 0.24]. In an exploratory assessment of OS, progression-free survival, and objective response rate, cabozantinib appeared to have a larger treatment effect in patients with RET M918T mutation-positive tumors compared with patients not harboring this mutation. For patients with RET M918T-positive disease, median OS was 44.3 months for cabozantinib versus 18.9 months for placebo [HR, 0.60; 95% CI, 0.38-0.94; P = 0.03 (not adjusted for multiple subgroup analyses)], with corresponding values of 20.2 versus 21.5 months (HR, 1.12; 95% CI, 0.70-1.82; P = 0.63) in the RET M918T-negative subgroup. Median treatment duration was 10.8 months with cabozantinib and 3.4 months with placebo.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 CABOZANTINIB:

a) Perforations and Fistulas: Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of cabozantinib-treated patients, respectively. All were serious and one GI fistula was fatal (< 1%). Non-GI fistulas including tracheal/esophageal were reported in 4% of cabozantinib-treated patients. Two (1%) of these were fatal.

b) Diarrhea: In one study, Diarrhea occurred in 74% of patients treated with cabozantinib. Grade 3 diarrhea occurred in 11% of cabozantinib-treated patients/

c) Hemorrhage: Serious and sometimes fatal hemorrhage occurred with cabozantinib. The incidence of Grade ≥3 hemorrhagic events was higher in cabozantinib-treated patients compared with placebo (3% vs. 1%).

d) Thrombotic Events: Cabozantinib treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in cabozantinib-treated and placebo-treated patients, respectively).

e) Wound Complications: Wound complications have been reported with cabozantinib.

f) Hypertension: Cabozantinib treatment results in an increased incidence of treatment-emergent hypertension with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (modified JNC criteria) stage 1 or 2 hypertension identified in 61% in cabozantinib-treated patients compared with 30% of placebo-treated patients in the randomized trial.

g) Osteonecrosis of the Jaw: Osteonecrosis of the jaw (ONJ) occurred in 1% of cabozantinib-treated patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery.

h) Palmar-Plantar Erythrodysesthesia Syndrome: Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 50% of patients treated with cabozantinib and was severe (≥ Grade 3) in 13% of patients.

i) Proteinuria: Proteinuria was observed in 4 (2%) of patients receiving cabozantinib, including one with nephrotic syndrome, as compared to none of the patients receiving placebo.

j) Reversible Posterior Leukoencephalopathy Syndrome: Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one (<1%) patient.

k) Drug Interactions: Avoid administration of cabozantinib with agents that are strong CYP3A4 inducers or inhibitors.

l) Hepatic Impairment: Cabozantinib is not recommended for use in patients with moderate or severe hepatic impairment.

m) Embryo-fetal Toxicity: Cabozantinib can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryo-lethal in rats at exposures below the recommended human dose, with increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

2.3.1.2: PEMBROLIZUMAB

a) Immune-Mediated Pneumonitis: Pembrolizumab can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving pembrolizumab, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of pembrolizumab in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

b) Immune-Mediated Colitis: Pembrolizumab can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Colitis occurred in 48 (1.7%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of pembrolizumab in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

c) Immune-Mediated Hepatitis: pembrolizumab can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Hepatitis occurred in 19 (0.7%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+

months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

d) Immune-Mediated Endocrinopathies: Hypophysitis: pembrolizumab can cause hypophysitis. Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

e) Thyroid Disorders: Pembrolizumab can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving pembrolizumab, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of pembrolizumab in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving pembrolizumab, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

f) Type 1 Diabetes mellitus: Pembrolizumab can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which has been reported in 6 (0.2%) of 2799 patients receiving pembrolizumab. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold pembrolizumab and administer antihyperglycemics in patients with severe hyperglycemia.

g) Immune-Mediated Nephritis and Renal Dysfunction: Pembrolizumab can cause immune-mediated nephritis. Monitor patients for changes in renal function. Nephritis occurred in 9 (0.3%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper.

Nephritis led to discontinuation of pembrolizumab in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients.

Other Immune-Mediated Adverse Reactions: Pembrolizumab can cause other clinically important immune-mediated adverse reactions. The immune mediated reactions may involve any organ system. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and 9 administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume pembrolizumab when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue pembrolizumab for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with pembrolizumab: arthritis (1.5%), exfoliative dermatitis, bullous pemphigoid, rash (1.4%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with pembrolizumab. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection in these patients.

h) Infusion-Related Reactions: Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving pembrolizumab. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

i) Embryofetal Toxicity: Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling the pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

2.3.2 KNOWN POTENTIAL BENEFITS

2.3.2.1: CABOZANTINIB:

A phase II randomized discontinuation trial assessed cabozantinib (XL184), an orally bioavailable inhibitor of tyrosine kinases including VEGF receptors, MET, and AXL, in a cohort of subjects with metastatic melanoma. Subjects received cabozantinib 100 mg daily during a 12-week lead-in. Subjects with stable disease (SD) per Response Evaluation Criteria in Solid Tumors (RECIST) at week 12 were randomized to cabozantinib or placebo. Primary endpoints were objective response rate (ORR) at week 12 and post randomization progression-free survival (PFS). Seventy-seven patients were enrolled (62% cutaneous, 30% uveal, and 8% mucosal). At week 12, the ORR was 5%; 39% of patients had SD. During the lead-in phase, reduction in target lesions from baseline was seen in 55% of evaluable patients overall and in 59% of evaluable subjects with uveal melanoma. Median PFS after randomization was 4.1 months with cabozantinib and 2.8 months with placebo (hazard ratio of 0.59; *P*=0.284). Median PFS from study day 1 was 3.8 months, 6-month PFS was 33%, and median overall survival was 9.4 months. The most common grade 3/4 adverse events were fatigue (14%), hypertension (10%), and abdominal pain (8%). One treatment-related death was reported from peritonitis due to diverticular perforation. The rest of reported studies are detailed in Section 2.2.2.

2.3.2.2: PEMBROLIZUMAB

The safety and efficacy of pembrolizumab were evaluated in Study KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial. Subjects were randomized to receive pembrolizumab at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Subjects with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging.

Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Subjects with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible.

Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent

central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration. A total of 834 patients were randomized: 277 patients to the pembrolizumab 10 mg/kg every 3 weeks arm, 279 to the pembrolizumab 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. The study demonstrated statistically significant improvements in OS and PFS for patients randomized to pembrolizumab as compared to ipilimumab.

Among the 91 subjects randomized to pembrolizumab 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to pembrolizumab 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Phase 1: To determine the recommended phase 2 dose (RP2D) of cabozantinib when administered orally in combination with intravenous pembrolizumab, in subjects with treatment naive advanced melanoma. **Phase 2:** To assess the preliminary efficacy of the established dose of cabozantinib in combination with pembrolizumab in subjects with treatment naive advanced melanoma.	**Phase 1:** Incidence of dose limiting toxicities. **Phase 2:** Best overall response rate (ORR) (complete response (CR) + partial response (PR)) per RECIST v1.1 with the established dose of cabozantinib in combination with pembrolizumab in subjects with advanced melanoma.	Phase 1: The combination of cabozantinib and pembrolizumab has not been tested in advanced melanoma. Therefore, the safety of this combination needs evaluation. Phase 2: The best overall response rate is a suitable endpoint for the initial phase 2 study.
Secondary		
Phase 1: To assess and describe the safety profile of the combination of cabozantinib and pembrolizumab. To assess and describe preliminary evidence of antitumor activity for cabozantinib in combination with pembrolizumab, in subjects with treatment naive advanced melanoma. **Phase 2:** To evaluate time to response from the combination of cabozantinib and pembrolizumab in subjects	**Phase 1:** To describe the safety profile of the combination of cabozantinib and pembrolizumab in subjects with advanced melanoma. ORR per RECIST v1.1 with the combination of cabozantinib and pembrolizumab in advanced melanoma. Time to response per RECIST v1.1. **Phase 2:** Best overall response rate (ORR) (complete response (CR) + partial	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
with treatment naïve advanced melanoma. To evaluate the disease control rate (DCR) with the combination of cabozantinib and pembrolizumab in subjects with treatment naïve advanced melanoma. To evaluate the progression-free survival from the combination of cabozantinib and pembrolizumab in subjects with treatment naïve advanced melanoma. To evaluate the overall survival with the combination cabozantinib and pembrolizumab in subjects with treatment naïve advanced melanoma.	response (PR)) per RECIST v1.1 criteria. Time to response per RECIST v1.1 criteria. DCR defined as the percentage of patients achieving CR + PR + SD at any time during the study following initiation of therapy. Radiologic progression-free survival (PFS) per RECIST v1.1 criteria. PFS is defined as the time between the first dose of study therapy and the earliest date of progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. Overall survival defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date).	
Tertiary/Exploratory		
Biomarker evaluation: To assess changes in tumor biomarkers.	Blood samples and biopsy samples will be collected to evaluate for biomarkers and changes in tumor microenvironment.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study is designed as a prospective trial to evaluate the combination of cabozantinib and pembrolizumab in adult patients with advanced melanoma who did not previously receive cabozantinib. Prior use of anti-PD-1 inhibitors is allowed in the adjuvant setting provided that the last dose is longer than 6 months prior to developing metastatic disease. Pembrolizumab will be used at the recommended approved dose for this indication.

This single institution, investigator-initiated trial has two phases: a phase 1b dose escalation of cabozantinib in combination with pembrolizumab, to establish the recommended phase 2 dose for the combination. The Dose Escalation Phase will utilize a 3+3 design over 3 planned dose levels leading to the identification of aR2PD and MTD for the combination of cabozantinib and pembrolizumab.

This will be followed by a single-arm, open label, phase 2 study testing a fixed dose of cabozantinib combined with the standard-dose immune checkpoint inhibitor pembrolizumab. The study is powered to a primary endpoint of best ORR with the combination of cabozantinib and pembrolizumab. Secondary endpoints include clinical benefit (DCR and duration of DCR), time to response, PFS, and OS. Enrollment for Part 2 will commence only after a RP2D is identified from phase 1.

Treatment will be administered on an outpatient basis. Cabozantinib will be administered orally daily, and pembrolizumab will be intravenous infusion once every 3 weeks. Reported adverse events and potential risks are described in section 2.3. Appropriate dose modifications are described in Section 6.1.2.3 No investigational or commercial cancer directed agents or therapies other than those described below may be administered.

Safety assessment will follow the guidelines provided in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version.4.03.

Subjects will be followed clinically on the D1 of each cycle and radio-graphically starting 12 weeks after initiation of treatment then every 12 weeks for tumor evaluation. Post-treatment scans will be compared to the baseline scan and responses will be assessed based using RECIST v1.1. Appendix A.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 PHASE 1:

“Combination” clinical trials of novel immunological/targeted therapeutic agents assess the safety and/or efficacy of a combination of immunotherapeutic agents. While this begins to address understanding the potential benefit of such combinations seen in pre-clinical models, it complicates the assessment of the safety and efficacy of the immunologic agents. Phase 1 dose-escalation trials are especially difficult, since subjects are generally treated at the MTD of the backbone immunologic therapy, which, by definition, already induces significant toxicity in approximately 1/6 of subjects (the target rate of the 3 + 3 dose-escalation trial

design). The phase 1b dose escalation trial of combination immunotherapy that addresses these issues by escalating against the effect of regimen-limiting toxicity (RLT), i.e., toxicity induced by the immunological agents in combination that is not seen with either agent alone (or seen at severities or rates of occurrence above expected from existing data) is a reasonable approach. Additionally, if one of the agents is already approved and considered a standard of care regimen for the indication being studied, additional toxicities (as for type, severity or timing) seen above those expected that limit the administration of the backbone therapy could also be considered an RLT.

Cohorts of 3 to 6 subjects will be enrolled at each dose level and each subject will participate in only 1 cohort. The starting dose level (dose level 0) will be cabozantinib 40 mg daily, and pembrolizumab 200 mg once every 3 weeks as per the package label. The first subjects at each dose level will be treated and observed for DLT through the DLT assessment period (Study Day 1-21). If there is no DLT observed (Section 4.3.2) in the group of 3 or more subjects, the next cohort will be enrolled, and escalation will proceed to the next dose (dose level 1) cabozantinib 60 mg daily and pembrolizumab 200 mg once every 3 weeks as per the package label.

If a DLT is observed in 1 subject in the first 3 subjects enrolled in a cohort, enrollment will proceed, and the cohort size will be increased up to 6 subjects. If only 1 DLT is observed in 6 subjects in a cohort, escalation will proceed, and the next cohort may begin enrollment.

A minimum of 3 subjects will be enrolled in each Cohort. The maximum allowed DLTs per cohort to allow subsequent dose escalation is 1 DLT observed in 6 subjects. The sponsor may also choose to enroll up to 6 subjects initially into a cohort. Dose escalation will proceed if no more than 1 DLT is observed in 6 subjects to the next dose level. The dose level 1 will be the maximum allowed dose.

If $\geq$ 2 of 6 subjects experience a DLT in any cohort, dose escalation will cease and the previous lower dose of cabozantinib may be designated the MTD and RP2D. If $\geq$ 2 of 6 patients experience a DLT in the Dose level 0, then a step cohort (Dose level -1) will be enrolled with cabozantinib administered daily at 20 mg daily and pembrolizumab 200 mg once every 3 weeks, as per the package label. However, the sponsor may also decide to investigate an additional lower or intermediate dose group(s) than have already been tested. In such a scenario, the protocol will be amended. Subjects will be enrolled and evaluated as described above for previous dose escalation cohorts except that staggered enrollment with a sentinel subject will not be required. Three to 6 subjects will be enrolled at the intermediate or lower dose and DLT assessments performed, with expansion to 6 subjects as required and applicable. A maximum of 0 DLTs in the first 3 subjects or 1 DLT in the first 6 subjects will define this dose as the MTD.

4.2.2 PHASE 2:

The phase 2 part of the study will be run in two stages. In the first stage, 14 subjects will be accrued. If there are 5 or fewer responses in these 14 subjects, the study will be stopped. Otherwise, 30 additional subjects will be accrued for a total of 44 subjects. This study design will have a limited enrollment of subjects to the trial if the combination does not show a

signal of activity in advanced melanoma.

4.2.3 BLINDING:

Blinding will not be performed as this is an open-label trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 PHASE 1B:

The Dose Escalation Phase 1b part will utilize a "3+3" design for escalation. The study plan includes the evaluation of 3 planned dose levels of cabozantinib administered orally. A minimum of 6 and a maximum of 18 subjects will be enrolled in each dose escalation cohort in Phase 1b, starting at 40 mg daily. The Sponsor reserves the right to adjust the planned cabozantinib dose levels based on emerging study data (Note: This will be considered as a protocol amendment) The planned cabozantinib dose levels to be studied in the Dose Escalation Phase 1b are presented in table 1. If the MTD has not been identified at the highest planned dose level, the Sponsor reserves the right to consider additional dose levels, and this would require a protocol amendment.

Table 1: Planned Dose Levels of Cabozantinib and Pembrolizumab

Dose Level	**Cabozantinib**	**Pembrolizumab**
-1	20 mg	200 mg
0 (starting dose)	40 mg	200 mg
1	60 mg	200 mg

Pembrolizumab will be administered at a standard recommended (drug label) dosing of 200 mg intravenously once every 3 weeks.

DLTs are defined in Section 4.3.2 Part 1 Dose Escalation: Dose-Limiting Toxicities (DLTs). The DLT rate across all subjects enrolled within a cohort in phase 1 must be <33% to allow escalation to the next dose level in that Arm. *The DLT observation period is 21 DAYS from date of first dose of cabozantinib.*

At the start of any new cohort, there will be a waiting period of at least 1 week after the first dose of the 3rd subject before enrollment of additional subjects into the same cohort. If a subject withdraws from the study prior to completion of the DLT assessment period for a reason other than a DLT, a replacement subject will be enrolled in that cohort.

Dose escalation in Part 1 to the next dose level can only occur after a minimum of 3 subjects have completed their DLT observation period for the current dose level, and the DLT rate does not exceed 33%.

Prior to escalation to a new dose level, the Safety Review Committee (SRC) will meet to review the safety data from the current cohort in order to determine if dose escalation is warranted.

The following rules govern dose escalation in Phase 1b:
• If none of the initial 3 subjects at a dose level experiences a DLT, escalation to the next dose level may occur. However, the Sponsor reserves the right to enroll up to 12 subjects in a cohort in order to obtain additional safety information.

• If 1 of the 3 initial subjects experiences a DLT, then 3 additional subjects will be enrolled in the same cohort (i.e., same dose level). If the DLT rate does not exceed 33% in the first 6 subjects, escalation to the next dose level may occur. However, the Sponsor reserves the right to enroll up to 12 subjects in a cohort in order to obtain additional safety information.

• If 2 or more subjects experience DLTs at a dose level, no further dose escalations will occur at that dose schedule. One or more lower dose level(s) may be tested in search of the MTD, defined as the dose level immediately below that in which ≥ 2 of 6 subjects experience DLTs.

4.3.2 PHASE 1B: DOSE-LIMITING TOXICITIES (DLTS)

Standard safety monitoring will be employed for DLT assessment and dose-escalation decisions. All AEs will be considered in DLT assessment unless an event is clearly unrelated to trial treatment. DLTs for phase 1b are defined below and only include AEs that are considered possibly, probably, or definitely related to the cabozantinib plus Pembrolizumab regimen which occur *during the first 21 days of therapy*. All AEs, including DLTs, are to be reported and graded using NCI CTCAE, Version 4.03.

The following AEs will be considered DLTs **if deemed related to study therapy**:

• Hematologic

o Asymptomatic Grade 4 neutropenia lasting for > 5 days.

o Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm3 with a temperature of ≥ 38.3 degrees C

o Grade ≥ 3 neutropenic infection

o Grade ≥ 3 thrombocytopenia with bleeding

o Asymptomatic Grade 4 thrombocytopenia lasting for > 5 days.

• Non-hematologic:

1. All non-hematologic Grade ≥3 adverse events at least possibly related to study treatment of any duration must be DLTs with the following exceptions:

i. Transient (≤72 hours) abnormal laboratory value without associated clinically significant signs or symptoms

ii. Nausea, vomiting, or diarrhea adequately controlled with supportive care within 48 hours

iii. Alopecia

iv. Grade 3 fatigue in a patient with Grade 1 or Grade 2 fatigue at baseline

v. hypertension

2. Any related ≥ Grade 3 AE which is unexpected in severity and/or duration compared to the known safety profiles of cabozantinib and pembrolizumab when used as single agents, and that cannot be managed by dose modification (reductions or interruption) and adequate supportive care, requires permanent discontinuation of cabozantinib and/or pembrolizumab.

3. Inability to take ≥ 75% of the total planned cabozantinib dose for the DLT Evaluation Period because of a treatment-related AE leading to dose reductions and/or interruptions.

4.3.3. PHASE 2: CABOZANTINIB WITH PEMBROLIZUMAB

After completion of the Dose Escalation Phase 1b, and the identification of a RP2D for cabozantinib in combination with pembrolizumab, subjects who meet the inclusion and exclusion criteria for Phase 2 part of the study will be treated with cabozantinib orally daily, and pembrolizumab once every 3 weeks per the dosing label, till disease progression or limiting toxicity.

4.4 END OF STUDY DEFINITION

At any time, the study may be terminated by the study sponsor, the sponsoring institution, or by Exelixis. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study and shall discontinue conduct of the study as soon as is medically practicable.

Procedures for withdrawal of individual patients can be found in Section 7.2

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

A patient must meet all of the following criteria to be eligible for enrollment (defined as receiving the first trial treatment) in the trial:

1. Histologically or cytologically confirmed unresectable in-transit (stage IIIc) or metastatic (stage IV) melanoma.
2. Must have at least 1 lesion that qualifies as a measurable (target) lesion per RECIST v1.1
3. Subjects must be willing to have blood draws for future biomarker testing as outlined in Section 11.9.
4. The subject has an ECOG performance score of ≤2 However; the phase 1b part will include only ECOG performance of 0-1 and life expectancy of >12 weeks
5. Aged 18 years and older.
6. The subject should not have received any treatment for advanced melanoma, EXCEPT, BRAF and/or MEK inhibitor. (2 week washout)
7. The subjects who have received adjuvant therapy including anti- PD-1 can be included in the study, if the last dose of the adjuvant treatment was ≥ 6 months prior to developing metastatic relapse.
8. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.
9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to taking the first dose of study medication, if. If the urine test is positive or cannot be confirmed as negative, then a serum test is required which must be negative for the patient to enroll. Women of childbearing potential (WOCBP) must be willing to use 2 medically acceptable methods of contraceptive from Day 1 through 120 days after the last dose of trial treatment. The 2 medically acceptable birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Male patients of reproductive potential must agree to use an adequate method of contraception from Day 1 through 120 days after the last dose of trial treatment. Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.
10. Able to swallow pills.
11. The subject must have recovered to baseline or ≤Grade 1 CTCAE v 4 from

toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and /or stable on supportive therapy.

5.2 EXCLUSION CRITERIA

A patient meeting any of the following criteria is not eligible to participate in this study:

1. Subject had prior treatment with any anti-PD-1, anti-PD-L1, or anti- PD-L2 agent for the treatment of advanced melanoma (although prior use in adjuvant setting is allowed if the last dose >6 months prior developing metastatic disease).
2. Subjects with diagnosis of ocular and mucosal melanoma
3. Subject had prior cabozantinib for any indication.
4. Subject who received any small molecule tyrosine kinase inhibitor within 2 weeks before first dose of study treatment.
5. Subject who has had chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of study drug, or who has not recovered to CTCAE Grade 1 or better from the AEs due to cancer therapeutics administered more than four weeks earlier.
6. Radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
7. Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug. (A patient in the Survival Follow up phase of an investigational agent where no further treatment is expected is eligible). Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.
8. Patient is on any systemic corticosteroid therapy (more than 10 mg daily of prednisone or equivalent) within one week before the planned date for first dose of randomized treatment or on any other form of immunosuppressive medication.
9. Patient has a history of a malignancy (other than the disease under treatment in the study) within 2 years prior to first study drug administration. This should exclude adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other in situ cancers. Shorter intervals can be considered after discussion with Sponsor.
10. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of study drug), have no evidence of new or enlarging brain metastases, neurologically asymptomatic and are off systemic steroids for at least two weeks.
11. Patient previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody or small molecule tyrosine kinase inhibitor.

12. Patient has an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement will not be excluded from the study.
13. Patient has an active infection requiring systemic therapy.
14. Patient has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Patient has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). Patients will be tested for hepatitis B or C infections during screening if they are considered by the investigator to be at higher risk for these infections and have not been previously tested.
16. Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
17. Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Patient is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study.
19. Patient has received a live vaccine within 30 days prior to first dose.
20. Patient requires concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel). Allowed anticoagulants are the following:
    1. Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
    2. Low-dose low molecular weight heparins (LMWH) are permitted.
    3. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
21. Patient has experienced any of the following within 3 months before the first dose of study treatment:
    a. Clinically significant hematemesis, hematuria or gastrointestinal bleeding
    b. Clinically significant hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood
    c. any other signs indicative of pulmonary hemorrhage
22. Present use or anticipated need for strong CYP3A4 inducers or inhibitors listed in the table below. **Patients may not have received a strong CYP3A4 inducer within 12 days prior to registration nor a strong CYP3A4 inhibitor within 7 days prior to**

registration. Because the lists of these agents are constantly changing, it is important to regularly consult a comprehensive list such as the one located at http://medicine.iupui.edu/clinpharm/ddis/.

Table 3: Strong CYP3A4 inducers or inhibitors

Inducers	**Inhibitors**	
dexamethasone	Boceprevir	Conivaptan
phenytoin	Indinavir	Itraconazole
carbamazepine	Nelfinavir	Ketoconazole
rifampin	Lopinavir/ritonavir	Mibefradil
rifabutin	Saquinavir	Nefazodone
rifapentin	Telaprevir	Posaconazole
phenobarbital	Ritonavir	Voriconazole
St. John's Wort	Clarithromycin	Telithromycin

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

a) Cardiovascular disorders including,

i) Congestive heart failure (CHF): New York Heart Association (NYHA) Class 3 (moderate) or Class 4 (severe) at the time ofscreening.

ii) Concurrent uncontrolled hypertension defined as sustained BP ≥150 mm Hg systolic (grade 2), or ≥ 90 mm Hg diastolic (grade 2) despite optimal antihypertensive treatment. (Note: If there is any BP measurement that is performed within the screening period that is < 150 mm Hg systolic and < 90 mm Hg diastolic, then BP does not meet definition of sustained.)

iii) Any congenital history of long QT syndrome.

iv) Any of the following within 6 months before the first dose of study treatment:

v) unstable angina pectoris

• clinically significant cardiac arrhythmias

• stroke (including TIA, or other ischemic event)

• myocardial infarction

• thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study

vi) Cavitating pulmonary lesions(s) or known endotracheal or endobronchial disease manifestation.

vii) Lesions invading or encasing any major blood vessels.

b) Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:

i) Any of the following within 28 days before the first dose of study treatment:

• intra-abdominal tumor/metastases invading GI mucosa (malignant abdominal

ascites does not constitute mucosal invasion)

• active peptic ulcer disease,

• inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis

• malabsorption syndrome]

ii) Any of the following within 6 months before the first dose of study treatment:

• history of 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 ago.

iii) GI surgery (particularly when associated with delayed or incomplete healing) within 28 days. Note: Complete healing following abdominal surgery must be confirmed prior to initiating treatment with cabozantinib even if surgery occurred more than 28 days ago.

c) Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy or concurrent evidence of intraluminal tumor involving the trachea and esophagus.

d) Moderate or severe hepatic impairment.

e) Other clinically significant disorders such as:

i) active infection requiring systemic treatment within 28 days before the first dose of study treatment

ii) serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment

iii) history of organ transplant

iv) concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment

v) Major surgery (eg, thoracotomy, removal or biopsy of brain metastasis) within 1 month before Week 1 Day 1. Minor surgery (eg, simple excision, tooth extraction) at least 10 days before Week 1 Day 1. Subjects with clinically relevant ongoing complications from prior surgery are not eligible. Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment

24. The subject has organ and marrow function and laboratory values as follows:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	<1,500/mm3/mcL
White blood cell count	< 2,500/mm3.
Platelets	<100,000/mm3 / mcL
Hemoglobin	<9 g/dL- transfusion of packed red blood cells allowed up to 7 days prior to D1.
Renal	
Serum creatinine	>1.5 X upper limit of normal (ULN), GFR <30 ml/min
Serum electrolytes	Serum phosphorus, magnesium, and potassium < LLN supplementation allowed if necessary.
Hepatic	
Serum total bilirubin	> 1.5 X ULN Patients with a total bilirubin > 1.5 X ULN will not be excluded if
	Direct bilirubin </= ULN
AST (SGOT) and ALT (SGPT) Albumin	> 2.5 X ULN < 2.8 g/dl
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	>1.3 X ULN. Patients on oral anticoagulation are excluded
Urine	Urine protein/creatinine ratio (UPCR) > 1 (113.2 mg/mmol) creatinine or 24-hr urine protein of >/= 1 g

Table 2: Laboratory values for exclusion:

25. Cardiovascular: The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >/= 500ms within 14 days before Cycle 1 Day 1. Ejection fraction on Echo or MUGA </= 45%. NYHA class >/= 3. Note: If a single ECG show a QTcF with an absolute value >/= 500 ms, two additional ECGs at intervals of at least 2 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.

5.3 LIFESTYLE CONSIDERATIONS

Dietary restriction: Subjects must be instructed NOT to ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during the study.

5.4 SCREEN FAILURES

The reason for screen failure will be documented clearly. If the reason for screen failure is reversible, then the patient can be considered for the rescreening if >1 month has been passed from the time of initial screening, after discussion with primary investigator and the trial

sponsor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at the Holden Comprehensive Cancer Center, of the University of Iowa Hospitals and Clinics. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at HCCC/UIHC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

6. STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This will be a single institution phase 1b/2 study of a combination of cabozantinib and pembrolizumab in previously untreated advanced melanoma.

6.1.1.1. PRETREATMENT EVALUATION:

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening. The following assessments will be conducted prior to subjects

receiving their first dose of cabozantinib on this protocol.

- Confirmed diagnosis of advanced melanoma (non-ocular, non-mucosal)
- Evaluate BRAF mutation status
- Full medical history and physical examination
- Full medication list
- Baseline tumor assessment with CT scan (or MRI) of the chest, abdomen, and pelvis with contrast. Tumor burden must be measured using RECIST 1.1.
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height
- Triplicate 12-lead electrocardiogram (ECG) within 14 days
- Performance status by ECOG
- Serum pregnancy test for women with childbearing potential
- Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST), Phosphorus, Magnesium, GGT and LDH
- Thyroid function tests (T3, free T4, TSH)
- Coagulation studies (PTT, PT/INR)
- Routine urinalysis
- Urine Protein/Creatinine Ratio
- Viral hepatitis B and C screen for subjects considered to be at risk by investigator.

6.1.2 DOSING AND ADMINISTRATION

6.1.2.1 DOSING:

Cabozantinib will be administered in a tablet form. The drug is taken continuously for 21 days or 3 weeks. This period of time is defined as one treatment cycle. Side effects are monitored, and dose modifications permitted as per a prescribed algorithm. Cabozantinib to continue per PI discretion.

A fixed dose of 200 mg of pembrolizumab will be administered via intravenous infusion Q3W for up to 2 years.

6.1.2.2 ADMINISTRATION:

Pembrolizumab 200 mg will be administered as a 30-minute infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

6.1.2.3 DOSE MODIFICATION AND INTERRUPTION:

Subjects will be monitored for AEs from the time of signing informed consent through 30 days after the last dose of cabozantinib and/or pembrolizumab treatment. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be graded by the investigator according to CTCAE v. 4.0.

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 study treatment. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- If the etiology of AEs is unclear the first dose reduction must be made to cabozantinib then pembrolizumab depending on toxicity profile
- Dose modification criteria for cabozantinib for phase 2 part of the trial will be finalized based on the final dosing selected from the phase 1 trial. Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table below, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for AEs may occur at any time per investigator discretion. If treatment is interrupted due to AEs for more than 6 weeks, patient will be taken off study unless the investigator deems there to be previous or ongoing clinical benefit.
- Dose interruptions for reason(s) other than AEs (eg, surgical procedures) can be longer than 6 weeks but require Sponsor approval. The acceptable length of interruption will depend on agreement between investigator and the Sponsor.
- Dose interruptions may occur in 2 ways:

  --**Within a cycle**: If dosing interruption and/or dose reduction occurs between Day 1 and Day 21 of a cycle (including protocol-specified windows), the cycle proceeds as planned.

  -- **Prior to the initiation of a new cycle**: If the investigator decides on day 1 of a new cycle that dose interruption should occur, that cycle may be delayed. When the investigator decides that dosing should resume, the day that the patient restarts drug will be day 1 of that new cycle. Re-escalation to any previous dose may be allowed at the discretion of the investigator no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a previous dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

Table 4: Dose Modifications of Cabozantinib for Treatment Related AEs

CTCAE v4.0	Recommended Guideline for Management
Grade 1 AEs	Supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be** adequately managed	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately.

Discontinue cabozantinib unless the following criteria are met:
<

- Subject is deriving clear clinical benefit as determined by the investigator.<
- Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

6.2 WARNINGS, PRECAUTIONS, AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS:

THE FOLLOWING ARE TO BE CONSIDERED AS GENERAL GUIDELINES. TREATING PROVIDER WILL MANAGE AS DEEMED CLINICALLY INDICATED.

6.2.1 CABOZANTINIB

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue/asthenia, anorexia, weight loss, skin rash including PPE syndrome, mucosal inflammation/stomatitis, and hypertension. Subjects may also experience medically important but less frequent adverse events including arterial and venous thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack, and myocardial infarction; severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, intraabdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).
Common laboratory abnormalities reported as AEs include ALT increased, AST increased, TSH increased, hypokalemia, hypomagnesemia, hypophosphatemia, hypocalcemia, lipase increased, and thrombocytopenia.

Please refer to the Investigator's Brochure for additional details.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely for all AEs. The predicted effective plasma half-life of cabozantinib is 99 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2-3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, since without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.
Cabozantinib should be discontinued for the following adverse events: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events (e.g MI, cerebral infarction), nephrotic syndrome, malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw (ONJ), and RPLS.

Management of gastrointestinal disorders, hepatobiliary disorders, hematological disorders, fatigue, anorexia, weight loss, skin disorders, hypertension, thromboembolic events,

proteinuria, QTc prolongation, hypophosphatemia and thyroid function disorders are presented in this section as these have been observed in previous studies with cabozantinib or represent common class effect toxicity. In addition, guidelines to minimize the risk for potential serious adverse events (SAEs) such as GI perforation, GI and non-GI fistula formation, hemorrhagic events, and osteonecrosis of the jaw (ONJ) are provided in this section.

Please refer to the Investigator's Brochure for additional practice guidelines and management recommendations for side effects potentially related to cabozantinib treatment; available information on potential risk of congenital, familial and genetic disorders; and guidelines on management of overdose of cabozantinib study treatment.

GASTROINTESTINAL DISORDERS

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

DIARRHEA

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/ antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced according to the table 5. When the diarrhea is controlled, retreatment with study treatment may be acceptable per investigator decision. In addition, general supportive measures should be implemented including continuous oral hydration, monitoring for and correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.

Table 5: Guidelines for management of Treatment-Emergent Diarrhea

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (eg, small lactose-free meals, bananas and rice)

	• Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (eg, stool sample for culture) : Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h -- Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose -- Diarrhea not resolving: Start and or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) Consider starting second line antidiarrheal or referral to gastroenterologist

NAUSEA AND VOMITING

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. Medications should be assessed for potential drug interactions (refer to the current version of the Investigator's Brochure for further details).

STOMATITIS AND MUCOSITIS

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated as clinically indicated. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

HEPATOBILIARY DISORDERS

Cabozantinib is not recommended for use in patients with moderate or severe hepatic impairment, as safety and efficacy have not been established.

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

1. For subjects who enter the trial with grade 1 ALT, AST or total bilirubin who experience a grade increase, consider having study treatment interrupted and/or dose reduced as outlined in Table 4 if hepatotoxicity is considered to be drug related.

2. For subjects with elevations of AST/ALT up to 5 × ULN at baseline (such as in the presence of liver metastases), dose modifications and interruption are not required if there are no progressive drug related changes in the aminotransferases (more than a doubling on serial LFT testing) and if there are no progressive drug-related elevations in serum total bilirubin concentration (more than a doubling on serial LFT testing if baseline value is >1.5 ULN) or coagulation factors. Cabozantinib treatment should be interrupted when drug-related transaminase increases are accompanied by progressive drug-related elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. If hepatic toxicity resolves during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose.

3. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment. Elevations > 3 × ULN of ALT or AST concurrent with > 2 × ULN total bilirubin without other explanation can indicate drug-induced liver injury and drug should be permanently discontinued.

Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. AEs which are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions.

HEMATOLOGIC DISORDERS

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.

Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. Results of such tests are to be forwarded to the local laboratory data management vendor.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.

FATIGUE

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded.

Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure.

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade≥ 3 fatigue despite optimal management, at the investigator's discretion.

ANOREXIA AND WEIGHT LOSS

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for

Grade ≥3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of cabozantinib may be re-escalated to the previous dose.

SKIN DISORDERS

WOUND HEALING AND SURGERY

Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. If clinically possible, Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME

PPES, also known as hand-foot syndrome, skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilation, protection of pressure-sensitive areas of hands and feet, and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early manifestations of hand-foot syndrome include tingling, numbness, mild hyperkeratosis and painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPES related to study treatment are presented in Table 6.

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

Table 6: Management of Treatment-emergent PPE Syndrome

CTCAE v.4.0	Action to be taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. Start urea 20% cream twice daily and clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily and clobetasol 0.05% cream once daily and add analgesics (eg, NSAIDs/GABA agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily and analgesics. Resume cabozantinib at reduced dose if PPE recovers to Grade 0 or 1. Discontinue subject from study if intolerable PPE recurs after dose reduction or does not improve within 6 weeks.
CTCAE, Common Terminology Criteria for Adverse Events; GABA, gamma-amino butyric acid; NSAID, non-steroidal anti-inflammatory drug; PPE, palmar-plantar erythrodysesthesia.	

HYPERTENSION

Hypertension has been reported in subjects treated with cabozantinib. Blood pressure should preferably be monitored in a constant position visit to visit in a relaxed setting. Treatment guidelines for hypertension deemed related to cabozantinib are presented below.

Grade 2 Hypertension (Systolic 140-159, Diastolic 90-99) Antihypertensive Therapy: Continue Cabozantinib and consider the following:

Step 1) Initiate LA dihydropyridine calcium-channel blocker treatment (such as amlodipine) and if needed, after 24-48 hours of treatment, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at the maximum dose of therapy.

Step 2) If BP still not controlled, consider adding another antihypertensive agent, a selective beta blocker, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, alpha beta blocker; increase dose of this drug as described in step 1.

Step 3) If BP still not controlled, consider adding a 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1.

Step 4) If BP still not controlled, consider either 1 dose reduction of cabozantinib or stopping cabozantinib.

NOTE: Stopping or reducing the dose of cabozantinib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.

Grade 3 Hypertension (Systolic ≥ 160 Diastolic ≥ 100), hold cabozantinib until systolic BP ≤ 159 and diastolic BP ≤ 99.

Antihypertensive Therapy: BP management is identical to that for grade 2 (see steps 1-4 above) with 2 major exceptions:

1) If systolic BP > 180 or diastolic BP > 110 and the patient is symptomatic: consider inpatient hospitalization and management as clinically indicated.

2) If systolic BP > 180 or diastolic BP > 110 and the patient is asymptomatic, 2 new anti-hypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).

NOTE: Stopping or reducing the dose of cabozantinib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.

Dose Modification: HOLD cabozantinib until systolic BP < 159 and diastolic BP < 99. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of cabozantinib or stopping cabozantinib. **HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP > 180 or diastolic BP > 110**, permanently discontinue cabozantinib or if BP is controlled, re-start cabozantinib at one lower dose level after consultation with the Study Chair.

Grade 4 Hypertension (life-threatening consequences of hypertension)

Antihypertensive Therapy: Optimal management in inpatient setting. Recommend ICU support and IV medication. STOP cabozantinib and notify hospital staff that stopping cabozantinib may result in a decrease in BP.

Dose Modification: Permanently discontinue cabozantinib or if BP is controlled, re-start cabozantinib at 1 lower dose level after consultation with the Study Chair.

THROMBOEMBOLIC EVENTS

Thromboembolic events are frequent in cancer patients due to procoagulant changes induced by the malignancy or anti-cancer therapy. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE and/or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparin (eg, LMWH) is established. (Note: Therapeutic anticoagulation with oral anticoagulants or oral platelet inhibitors such as clopidogrel is not allowed in this study). Cabozantinib treatment may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated, they are deriving benefit from study treatment, and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment. During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests according to institutional guidelines. Results of such tests are to be forwarded to the local laboratory data management vendor. If there are any signs of clinically relevant bleedings, cabozantinib treatment should be interrupted immediately. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator.

Arterial thrombotic events (eg, transient ischemic attack, myocardial infarction) 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. Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

PROTEINURIA

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 8 provides treatment guidelines for proteinuria deemed related to cabozantinib.

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

Table 8: Management of Treatment associated Proteinuria

Severity of Proteinuria (UPCR)	**Action To Be Taken**
≤ 1 mg/mg (≤ 113.1 mg/mmol)	-- No change in cabozantinib treatment or UPCR monitoring
> 1 and < 2.0 mg/mg (> 113.1 and < 226.2 mg/mmol)	-- No change in cabozantinib treatment -- Consider confirming with a 24-hour urine protein assessment within 7 days (+/- 3 days). -- Consider monitoring UPCR once every week (+/- 3 days until UPCR < 1 on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times.
≥ 2.0 mg/mg (≥ 226.2 mg/mmol)	-- Hold cabozantinib treatment pending repeat UPCR and/or 24-hour urine protein. -- If ≥ 2.0 on repeat (UPCR or 24-hour protein), continue to hold cabozantinib treatment and check UPCR every week (+/- 3 days). If UPCR decreases to < 2, restart cabozantinib treatment at a reduced dose and continue monitoring UPCR once weekly (+/- 3 days) until the UPCR decreases to < 1.
Nephrotic syndrome	Discontinue cabozantinib treatment

CORRECTED QTC PROLONGATION

In accordance with clinical practice ECGs will be collected during this study. Only subjects with a baseline QT corrected by Fridericia (QTcF) ≤500 ms are eligible for this study. Subjects will have ECGs performed at times designated by the protocol: triplicate at screening, and single ECGs at monthly visits.

If at any time on study there is an increase in QTcF interval to an absolute value > 500, two additional ECGs must be performed, within 30 minutes after the initial ECG (each with intervals at least 2 minutes apart).

If the average QTcF from the 3 ECGs is > 500 ms, the following actions should be taken: Withhold study treatment. Repeat ECG triplicates hourly (+- 15 minutes) until the average QTcF is ≤ 500 ms, or otherwise determined by consultation with a cardiologist or appropriate expert.

- Interrupt cabozantinib treatment.
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management. Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved.
- Consider cardiology consultation for asymptomatic subjects for evaluation and management.
- Check electrolytes, especially magnesium, calcium, and potassium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (see http://www.qtdrugs.org)

Cabozantinib treatment may be restarted 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 ms is not confirmed.
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks (+/- 5 days), then every 2 weeks (+/- 5 days) for 1 month, then according to the protocol-defined time points.

Study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of cabozantinib-related QT interval prolongation and cannot be addressed with dose interruption and/or reductions.
- Persistent recurrence of cabozantinib-related QTcF after reinitiation of study treatment after two dose reductions.

ELECTROLYTE DISORDERS Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines in the section 6.1.2.3.

THYROID FUNCTION DISORDERS

Preliminary data from ongoing studies indicate that treatment-emergent elevation of thyroid stimulating hormone (TSH) by cabozantinib may be dose-dependent. Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia, hyperglycemia, and hypoglycemia, and associated laboratory changes, have been observed in single agent cabozantinib studies. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is recommended. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

HEMORRHAGIC EVENTS

Hemorrhagic events including serious and sometimes fatal events have been reported with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor in the lung with cavitary lesions or tumor lesions which invade or encase major blood vessels. NSCLC with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. Thus, the anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation.
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis, hematemesis, or hematuria

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or persistent, clinically significant hemoptysis or hematemesis

GI PERFORATION/FISTULA AND NON-GI FISTULA FORMATION

GI perforation/fistula and non-GI fistula formation have been reported with cabozantinib. Carefully monitor for episodes of abdominal pain, nausea, emesis, constipation, and fever especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

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

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

OSTEONECROSIS

Osteonecrosis of the jaw (ONJ) has been reported with use of cabozantinib. Additional risk factors for ONJ have been identified such as 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 ONJ.

Performing an oral examination is recommended prior to initiation of cabozantinib and periodically during cabozantinib therapy. Advise patients regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in patients receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be held for approximately 4 weeks prior (+/- 7 days) to a dental procedure and resumed after complete healing has occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by Exelixis on a case-by-case basis.

6.2.2 PEMBROLIZUMAB:

DIARRHEA:

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

- In patients with severe enterocolitis, permanent discontinuation of pembrolizumab should be considered and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- In patients with moderate enterocolitis, pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

NAUSEA/VOMITING

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

ANEMIA:

Transfusions may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concurrent medications.

NEUTROPENIA:

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

THROMBOCYTOPENIA:

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

ANTI-INFECTIVES:

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given

infectious condition, according to standard institutional practice.

IMMUNE-RELATED ADVERSE EVENTS:

Patients who develop a G2 or higher irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the SPONSOR. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

PNEUMONITIS:

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in table below:

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - o Improvement occurs in ≤2 weeks-dose of pembrolizumab, keep the same dose.
  - o May increase dosing interval by one week in subsequent cycles if improvement occurs >2 weeks.
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis ≥ Grade 2.

Table 9: Approach to Pneumonitis from pembrolizumab

Study drug associated pneumonitis	**Treatment**	**Supportive care**
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab, may return to treatment if improves to grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue pembrolizumab.	Systemic corticosteroids are indicated.

6.3 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.3.1 ACQUISITION AND ACCOUNTABILITY

Drug accountability and subject compliance will be assessed with drug dispensing and return records.

Study Drug Accountability: The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.3.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The identities and instructions for administration, storage, and handling of cabozantinib and pembrolizumab are described below. Both Cabozantinib and pembrolizumab are considered as, and referred to as, trial drug(s) or trial treatment in this protocol.

Cabozantinib: Chemical Name: *N*-(4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1- dicarboxamide, (2S)-hydroxybutanedioate
Cabozantinib Tablets (XL184): Exelixis will provide investigator with adequate supplies of cabozantinib, which will be supplied as freebase 60-mg, and 20-mg yellow film-coated tablets. The 60-mg tablets are oval, and the 20-mg tablets are round. See Exelixis Study Pharmacy Manual.

Schedule, route of administration and dose: Subjects will receive cabozantinib orally. The cabozantinib dosing will vary according to the dosing levels in phase 1b and the final decided dose for phase 2 pare of the trial. In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines.

Pembrolizumab [Keytruda® (US)], (commercially available) a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of cancer. Pembrolizumab may be supplied in 2 different formulations:

> Pembrolizumab injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and water for injection, USP.

OR

- Pembrolizumab powder for solution for injection is a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use glass vial

containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder, and free from visible foreign matter.

6.3.3 PRODUCT STORAGE AND STABILITY

All study medications will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations. Cabozantinib must be stored at room temperature. The tablets are meant to be taken PO only and not be crushed from dissolving in liquid or administered through other routes including PEG tube.

6.3.4 PREPARATION

Cabozantinib capsules and tablets are meant to be taken orally only and not to be opened or crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib capsules and tablets should not be administered to subjects who do not have adequate swallowing capacity. Cabozantinib is meant to be taken without food (subjects should not eat for at least 2 h before and at least 1 h after taking cabozantinib) with a full glass (at least 8 ounces or 240 mL) of water. If a dose is missed, the missed dose should not be taken less than 12 h before the next dose.

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study is non-randomized and open label.

6.5 STUDY INTERVENTION COMPLIANCE

The investigator will maintain accurate records of receipt of all the study medications, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.6 CONCOMITANT THERAPY

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over the counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and is radiation is NOT administered for tumor control. Cabozantinib should be held during the course of palliative radiotherapy and

resumed 1 week after completion of palliative radiotherapy. The specifics of the radiation treatment, including the location, will be recorded. All concomitant medications received within 30 days before the first dose of trial treatment through 30 days post last dose or until new treatment is started, whichever occurs first should berecorded.

6.6.1 RESCUE MEDICINE

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Nausea/vomiting: Administration of prophylaxis for nausea and vomiting should be administered per institutional guidelines and local standard practices for the standard of care chemotherapies\ offered for the control arm. For pembrolizumab, the therapy is considered to be of low to moderate emetogenic potential. Consideration for chemo induced nausea and vomiting prophylaxis should be given in subsequent cycles of the administration according to standard institutional practice and should not be routinely administered prior to the initial trial treatment of pembrolizumab. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

Anemia: Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin.

Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this trial. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.

Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

Events of Clinical Interest with a potential immunologic etiology (ECI): Please see the separate guidance document in the administrative binder regarding identification, evaluation and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an ECI, oral or intravenous treatment with a corticosteroid should be

considered, in addition to appropriate symptomatic treatment of a given condition.

6.6.2 SUPPORTIVE CARE GUIDELINES

IMMUNE-RELATED ADVERSE EVENTS (IRAE)

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These immune related adverse events (irAEs) may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Attention should be paid to AEs that may be suggestive of potential irAEs.

Table 10: Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires infusion interruption but responds	Stop Infusion.	Subject may be premedicated 1.5h (± 30-minutes) prior to

promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3**: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4**: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

6.6.3 ALLOWED THERAPY

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
  - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
  - *Therapeutic doses of LMWH* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 6 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.
  - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.2.
  - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction).

For restrictions on oral anticoagulants see 5.2.

6.6.4 PROHIBITED OR RESTRICTED THERAPY

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).
- Any non-protocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

  Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

6.6.5 POTENTIAL DRUG INTERACTIONS WITH CABOZANTINIB

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

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Treatment with cabozantinib and pembrolizumab may continue until one of the following events occurs:

- Documented disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences.
- Need for >2 dose delays due to the same toxicity as per the dose modification guidelines described.

- Patient withdraws consent
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The SPONSOR should be included in this decision.
- Patient is lost to follow-up
- Pregnancy in patient

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients may withdraw from the study at any time. Patients who discontinue early should return within 30 days (+/- 7 days) of the last dose of the study drugs for a follow-up evaluation. Any assessments listed for the final visit in Table will be performed at that time.

In addition, any of the following conditions require the withdrawal of the subject from study treatment:

− An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from treatment

_ The investigator believes it is not in the best interest of the subject to continue on study

− Necessity for treatment with other investigational drug or other anticancer medications prohibited by protocol

− Noncompliance with the protocol schedule

− Participation in another clinical study using anticancer agent(s)

− Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol

− Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 3 months following discontinuation of study treatment

− Women who become pregnant or are breast feeding

− Inability to tolerate cabozantinib

− Cabozantinib treatment delays > 6 weeks unless the subject was unequivocally benefitting from cabozantinib treatment

− Progressive disease (PD) as determined by the investigator. However, patients who continue to derive clinical benefit from cabozantinib and pembrolizumab as judged by the investigator may continue therapy despite radiographic progression of the disease.

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol-specified follow-up procedures and end-of-treatment assessments, if possible, unless consent to participate in the study is also withdrawn.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter

should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic. If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

Patients that withdraw from study treatment (but not their consent for follow-up) for reasons other than progression will continue to have scans per study calendar until PD is noted.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for [specify number of visits] scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The trial coordinator will attempt to contact the participant and reschedule the missed visit, at the earliest available appoint and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator and trial coordinator will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The intention of the study design is to closely monitor patients with safety follow-up and disease assessments in the absence of disease progression or other study discontinuation criteria.

For the purposes of this study, patients should be re-evaluated after the first 12 weeks of treatment and then every 12 weeks. **In addition to a baseline scan, confirmatory scans will** also be obtained at least 4 weeks and no more than 14 weeks following initial documentation of partial or complete response.

Primary efficacy endpoint is best ORR defined as the proportion of all treated subjects whose best response at any time during the study following initiation of therapy is confirmed CR or confirmed PR. This will be assessed according to the RECIST v1.1.(Appendix A).
PFS, defined as the time between the first dose of study therapy and the earliest date of progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. The endpoint ORR and PFS will be assessed according to the RECIST v 1.1 criteria.

Additional efficacy endpoints will include the disease control rate (DCR) defined as the percentage of patients achieving CR + PR + SD at any time during the study following initiation of therapy. This will be assessed according to RECIST v1.1 criteria. The duration of response (DOR), is defined as the time between the date that the criteria are first met for CR or PR or SD and the earliest date of progression or death.

OS, defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date), will also be analyzed.
The tumor assessment (TA) performed during screening will be used as a baseline for efficacy assessments. CT/MRI imaging of the chest and abdomen is required at Screening and at each TA, regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans in subjects where there is clinical suspicion of deep soft tissue metastases (eg, lesions in the thigh). Such additional CT/MRIs will be required at Screening when deep soft tissue disease is known/suspected and must be consistently repeated at all TAs if a deep soft tissue lesion is identified during Screening.

The same imaging modality must be used for all TAs, unless contraindicated. Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen is preferred. If not available, MRI can be used; however, a measurable lesion must not have the longest diameter smaller than 10 mm by MRI (10 mm on spiral CT). IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast maybe used, or MRI should be used at the Screening exam and at all TA time points. Subjects who develop contrast allergy after study enrollment must be followed by MRI for subsequent tumor measurements.

Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g., from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

If bone lesions are identified at any time during the study, additional imaging studies of the lesion(s) must be performed to confirm the malignant nature of the new findings on the bone scan. If an abnormal bone scan is observed at any time point throughout the study, a repeat bone scan must be performed prior to the confirmation of a CR (e.g., the remaining metastatic lesions must have resolved. In case of new lesions such as pleural effusion, cytology must be performed to identify and confirm malignancy. Skin and soft tissue lesions will be captured as non-measurable lesions through physical examination only.

Any subject who develops an objective tumor response (CR or PR) should undergo a second scan for confirmation at least 4 weeks later (and no more than 14 weeks). For subjects with progression (PD) consider confirmatory scans at least 4 weeks (and no more than 14 weeks) from the prior scan in order to verify the reliability of the radiologic findings.

Definition of Measurable / Non-measurable Lesions

- -Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter > 20 mm and the other dimension > 10 mm on MRI, or 10 mm x 10 mm for spiral CT. The area will be defined as the sum of the largest diameter with its perpendicular.

- Non-measurable (evaluable) lesions are all other lesions, including unidimensional measurable disease and small lesions (lesions without at least 1 diameter > 20 mm on MRI, or > 10 mm on spiral CT), and any of the following: lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions. All measurable and non-measurable lesions should be assessed at Screening and at the defined TA time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

Definition of Target / Non-Target Lesions

At Screening, measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, must be identified as Target lesions to be measured and recorded on the CRF. The Target lesions should be representative of all involved organs. In addition, Target lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the of diameters for all index lesions will be calculated. This baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at each TA.

Measurable lesions, other than target lesions, and all sites of non-measurable disease, will be identified as non-target lesions. Non-target lesions will be recorded on the CRF and will be evaluated at the same assessment time points as the target lesions. In subsequent assessments, non-target lesions will be recorded as CR, stable, orprogression.

8.2 SAFETY AND OTHER ASSESSMENTS

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the

adverse experience to the single agent. The details of classification of adverse events is provided in Section 8.3.3

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Sponsors' product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event is any adverse event occurring at any dose or during any use of Investigation product/s that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose;
- Is another important medical event

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

An investigator who is a qualified physician will evaluate all adverse events as to:

CTCAE V 4.0	
Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences: urgent intervention indicated.
Grade 5	Death related to AE

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.

The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):

Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
Rechallenge	Was the subject re-exposed to the Sponsor's product in this study?

	If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
	The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
Record one of the following: **Yes,** there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.3.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

8.3.4.1. TREATMENT PERIOD

Patients will be asked to visit the clinic every three weeks. Treatment will continue until disease progression or significant toxicity. The details of on-treatment assessments can be found in Section 1.3

8.3.4.2 End of treatment and premature withdrawal visit

Required observations following the completion of protocol therapy: Follow-up visits may be performed +/- 7 days from the targeted study visit date. Laboratory evaluations may be collected up to 24 hours prior to study visit without being a deviation.

Patients will be followed for survival and progression every 3 months for 2 years, every 6 months for 3 years and yearly until death. Follow-up will be performed using telephone contact, correspondence with treating physicians, and death records as necessary to update vital status.

Adverse events	Capture all AEs observed for 30 days after last dose of treatment. After 30 days, only SAEs that are at least possibly attributed to the study drug are required to be captured
Concomitant medications	Capture all concomitant medications for 30 days after last dose of treatment or until a new treatment is started, whichever occurs first.

8.3.5 ADVERSE EVENT REPORTING

See section 11.6

8.3.6 SERIOUS ADVERSE EVENT REPORTING

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures, from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs that are assessed by the PI as **related** to the combination therapy or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

All grade 4 adverse events noted among other patients in this study, or other studies with this combination will be notified to other patients enrolled in the study.

8.3.8 EVENTS OF SPECIAL INTEREST

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for any of the treatments: five times the pembrolizumab dose or more than 20% of the dose of cabozantinib. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab or the cabozantinib regimen should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

8.3.9 REPORTING OF PREGNANCY

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or

outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in theresearch); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, oroutcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 working days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Phase 1:

The primary objectives are to assess safety and determine the recommended Phase II dose cabozantinib in combination with the standard of care, pembrolizumab. There are no primary efficacy endpoints for Phase I.

Phase 2:

The primary objective is to determine whether treatment with combination cabozantinib and pembrolizumab will increase the objective response rate (ORR) in patients with advanced melanoma compared to historic estimates for patients treated with pembrolizumab monotherapy. Historic ORR in patients treated with pembrolizumab monotherapy is reported to be approximately 35% [N Engl J Med. 2015 Jun 25;372(26):2521-32]. We anticipate the addition of cabozantinib will increase the ORR to 55%. In statistical terms, we are testing the null hypothesis H_0: ORR $\leq$ 35% versus the alternative hypothesis H_1: ORR $\geq$ 55%.

- Secondary Efficacy Endpoint(s):

There are no formal and testable hypotheses for secondary endpoints.

9.2 SAMPLE SIZE DETERMINATION

Phase 1:

Phase I will utilize a standard 3+3 dose escalation design. A minimum of 6 and a maximum of 18 evaluable patients are required.

Phase 2:

When testing the null hypothesis that the ORR $\leq$ 35% versus the alternative hypothesis that the ORR $\geq$ 55%, a sample size of 44 evaluable patients will ensure 80% power to detect a 20% absolute increase in ORR using an optimal Simon's two-stage design (Simon, 1989). Power estimates are based on an alpha = 0.05.

Based on historical trends our institution, the anticipated accrual rate is 2-3 patients per month.

9.3 POPULATIONS FOR ANALYSES

The safety population will include all enrolled patients who receive at least 1 dose of both cabozantinib and pembrolizumab. The safety population will be the analysis population for the safety analyses.

The modified intention-to-treat (mITT) population will comprise all patients who receive at least 1 dose of both pembrolizumab and cabozantinib, and who have baseline and at least 1 post-baseline imaging assessment. The mITT is the analysis population for the efficacy analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by count and proportion.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Phase I:

There are no primary efficacy endpoints for Phase I. The recommended Phase II dose is defined as the highest dose level for which at most 1 out of 6 patients experience a DLT.

Phase II:

The primary efficacy endpoint is ORR. ORR is defined as the proportion of patients with RECIST disease response (CR, PR). All patients that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

Phase II is utilizing an optimal Simon's two-stage design. As such, 14 patients will be enrolled in the first stage. If 5 or fewer patients respond (CR or PR), the study will be terminated due to futility. Otherwise, an additional 30 patients will be enrolled in the second stage. As per the decision rules of the design, the null hypothesis will be rejected if at least 21 patients respond (CR or PR) out of the 44 total patients. The ORR and 95% exact confidence interval will be reported.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary efficacy endpoints (DCR, PFS and OS) will be summarized descriptively using the mITT population.

DCR

DCR is defined as the proportion of patients with RECIST disease control (CR, PR, or SD). All patients that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders. A binomial proportion with 95% exact confidence interval will be reported.

PFS

PFS will be defined as the time from treatment initiation to the date of first documentation of disease progression or death due to any cause in the absence of documented progression. For patients who discontinue study treatment due to reasons other than progression or death, the patient will be censored at their last radiographic assessment for progression. Cumulative PFS will be descriptively summarized over time with the method of Kaplan-Meier.

OS

OS will be defined as the time from treatment initiation to the date of death due to any cause. Cumulative OS will be descriptively summarized over time with the method of Kaplan-Meier.

9.4.4 SAFETY ANALYSES

The incidence of treatment-emergent adverse events will be summarized by system organ class and/or preferred term, type of adverse event, severity (based on NCI CTCAE v4.03 grades), and relation to study treatment using the safety population. The most severe grade per patient will be reported. Elapsed days of toxicity will be summarized with descriptive statistics. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent adverse events will be presented in tabular form. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be presented to characterize the patient population. No inferential statistics will be conducted since this is a one-arm trial.

9.4.6 PLANNED INTERIM ANALYSES

No interim efficacy analyses are planned.

9.4.7 SUB-GROUP ANALYSES

No subgroup analyses are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

9.4.9 EXPLORATORY ANALYSES

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Potential subjects will be recruited from patients seen in the Clinical Cancer Center at

University of Iowa Hospitals and Clinics who appear to be eligible for the study. A member of the research team will meet with the patient to go over the informed consent document and answer any questions they may have. Other potential treatment options, whether investigational or standard of care, will be discussed with the patient. The patient will be given the time they need to make their decision; they are encouraged to discuss it with their family and/or friends. If the patient decides to participate, they will need to sign the consent form during one of their clinic visits. No study-specific procedures will be performed before the informed consent document is signed.

To avoid coercion, potential patients will be informed that they are free to refuse to participate in the trial, and that refusing to participate will not affect the availability of future medical care at UIHC. A copy of the signed informed consent document will be given to the patient.

10.1.2 TABULATION OF INDIVIDUAL PARTICIPANT DATA

The investigator must maintain detailed records of all trial participants who are enrolled in the trial or who undergo screening. Source documents include, but are not limited to, patient medical records and investigator's patient trial files, as well as all test results.

The following minimum information should be entered into the enrolled patient's source documents:

- The date the patient entered the trial and the patient number
- The trial protocol number
- The date that informed consent was signed
- Evidence that the patient meets trial eligibility requirements (eg, medical history, trial procedures, evaluations)
- The dates of all trial-related patient visits
- Evidence that trial-required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of trial medication accountability
- Occurrence and status of any AEs
- The date the patient exited the trial, and a notation as to whether the patient completed the trial or was discontinued early, including the reason for discontinuation
- Any deviations from the protocol

10.1.3 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects will be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to Exelixis and its partners or designees for review.

10.1.4 PUBLICATIONS OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide Exelixis with a copy of any proposed publication or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts and also comply with any provisions regarding publication that are agreed to between the PI's institution (eg, institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

11.0 TRIAL-SPECIFIC DATA AND SAFETY MONITORING PLAN

Type of Clinical Trial:

❒ Investigator-initiated (UI/HCCC)
❑ Investigator-initiated, participating site
❑ Pilot study
❑ Phase I
❒ Phase I/II
❑ Phase II
❑ Phase III
❑ Compassionate-use/Expanded Access
❒ Interventional Treatment
❑ Interventional Non-Treatment
❑ Non-Interventional

Study risk-level:

❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
❑ Level 2—risk of death* <1% or any adverse event 1% –5%
❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
❒ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
❑ Drugs being used on a "compassionate" basis

** Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:
All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore data export

Selected monitoring strategy based on risk-level:

Risk Level 4
Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review
An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements:
- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.

- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent,
  - determine compliance with protocol's study plan,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy of data in the research record with the primary source documents,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting
For non-serious Adverse Events, documentation must begin from the time the informed consent document is signed through the 30-day follow-up period after study drug is discontinued.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting
For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

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

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct

normal life functions

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

FDA Reporting Requirements (for Sponsor-Investigators)
It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571. See Instructions for completing Form 3500A. Please note all instance of UIHC, location, and faculty / staff should be redacted from supporting documentation and the 3500A.

The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

For detailed explanation of the above definitions, requirements, and procedures related to IND application safety reports and the responsibilities of IND applications sponsors with regard to such reporting, refer to Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (PDF - 227KB)

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known (grading the event per CTCAE)
- Supportive laboratory results and diagnostics
- Sponsor-Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Data Monitoring and Management

Subject Registration
All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.

- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

Subject Data
For HCCC investigator-initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

Forms Monitoring
OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

Final Reports
A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

11.6 ROUTINE ADVERSE EVENT REPORTING

For non-serious Adverse Events, documentation must begin from the time the informed consent document is signed through the 30-day follow-up period after study drug is discontinued.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's

Common Toxicity Criteria (CTCAE)4.04), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.11.7 Serious Adverse Event Reporting.

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30-day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- 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).

11.7.1 EXELIXIS REPORTING

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures, from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs that are assessed by the PI as **related** to drug or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

11.7.2 REGULATORY REPORTING

The Investigator will assess the expectedness of each related SAE. The current cabozantinib/ pembrolizumab Reference Safety Information (Appendix K of the most recent approved

Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib or pembrolizumab. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;
- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.
- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The PI shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

11.8 DATA MONITORING AND MANAGEMENT

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Subject registration includes the following:

- Consent date and the IRB approved consent used
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

Subject Data
In addition to the subject registration and subject status data entered in OnCore for all HCCC trials, research staff also enters the subject study data into electronic case report forms (eCRFs) for HCCC investigator initiated studies. eCRFs are approved by the PI and statistician prior to study activation to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are generally maintained in the subject's file. eCRF data are expected to be entered into OnCore within 30 calendar days after a subject's study visit.

Forms Monitoring
OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all mandatory fields are entered completely, accurately and within time requirements. The assigned DSMC monitor manages the logistics associated with the data monitoring review. Once the clinical trial is identified for monitoring, the monitor arranges for a selection of cases to review from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries within the eCRF to resolve missing, incomplete and/or incorrect information. A member of the research team is expected to respond to monitoring queries within 14 business days.

This process can often identify a misunderstanding or deficiency in protocol requirements early in the study and can improve data quality.

Final Reports
A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

11.9 SPECIMEN COLLECTION FOR BIOMARKER TESTING

PHASE II (EXPANSION) ONLY

Archival Tumor Tissue: A sample of archival tumor tissue will be obtained at baseline on all patients enrolled in the expansion portion for biomarker studies, if available.

Blood samples: 5 tubes of blood will be drawn in unheparinized tubes, spun and stored at -80 c for future biomarker studies. Samples will be drawn at the same time as standard of care labs at baseline, week 7 (+/- 1 week) and at time of progression for a select number of patients enrolled in the expansion portion of the study.

Optional Fresh Biopsy: For select patients, tumor tissue samples (fresh) will be obtained at baseline, week 7 (+/- 1 week) and progression for subjects who consented to optional samples at time of consent during the expansion portion of the study and have superficial lesions (skin/lymph nodes). Tissue samples will be flash frozen and stored at -80 C to be processed later for biomarker testing. Recommend: Per PI discretion, Cabozantinib be held for 4 days prior to biopsy and restarted 7 days after biopsy provided adequate wound healing is achieved.

Number of patients: 10-15

Tests: IHC: Angiogenic and Immune markers: Expansion Phase

Timeline:

	Baseline	At 7 weeks +/- 1 week	At progression
Tissue (core biopsy)	X	X	X
Peripheral blood (for biomarker studies)	X	X	X

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13. PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

Protocol Appendix A- Recist 1.1 Quick Reference

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.**

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- 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.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- 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 when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of “Target” and “Non-Target” lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and 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 (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

Protocol Appendix B- 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.

Protocol Appendix C- CABOZANTINIB MEDICATION DIARY

CYCLE NUMBER	
NUMBER OF PILLS DISPENSED	
DAILY DOSE	
NUMBER OF PILLS RETURNED	
NUMBER OF PILLS EXPECTED TO BE TAKEN THIS CYCLE	
ACTUAL NUMBER OF PILLS TAKEN THIS CYCLE	
EXPLANATION FOR DISCREPANCY IN COUNT	

PILL COUNT TO BE COMPLETED BY RESEARCH COORDINATOR

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS:

1. **Cabozantinib should be taken orally without food. Do not eat from atleast 2 hours before through 1 hour after each dose of cabozantinib.**
2. **Cabozantinib should be taken at approximately the same time every day. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose**
   a. **If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled**
   b. **Remember to record missed doses**
3. **If vomiting occurs after taking cabozantinib, do not take a replacement dose on that day. Resume at the next scheduled dose**
   a. **If it appears that an intact tablet has been expelled do not take a replacement dose that day**
   b. **If consistent vomiting occurs please notify the study investigator**
4. **Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided while taking Cabozantinib.**
5. **Cabozantinib tablets should be stored at room temperature.**
6. **RETURN ALL EMPTY BOTTLES AND LEFTOVER PILLS**

DAY	MEDICATION	DATE	TIME		NUMBER OF TABLETS		COMMENTS
					20 MG	60 MG	
EXAMPLE	*CABOZANTINIB*	*08/01/2018*	*9:00*	*AM*	*3*	*0*	
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							

PATIENT
SIGNATURE_____DATE_____

REASEARCH
COORDINATOR_____DATE_____