PROTOCOL

Phase 2 Study of cabozantinib combined with pembrolizumab in metastatic or recurrent gastric and gastroesophageal Adenocarcinoma (mGC)

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Study Drug: Cabozantinib [Cabometyx©]

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How is the Agent Supplied?: Exelixis, Inc.

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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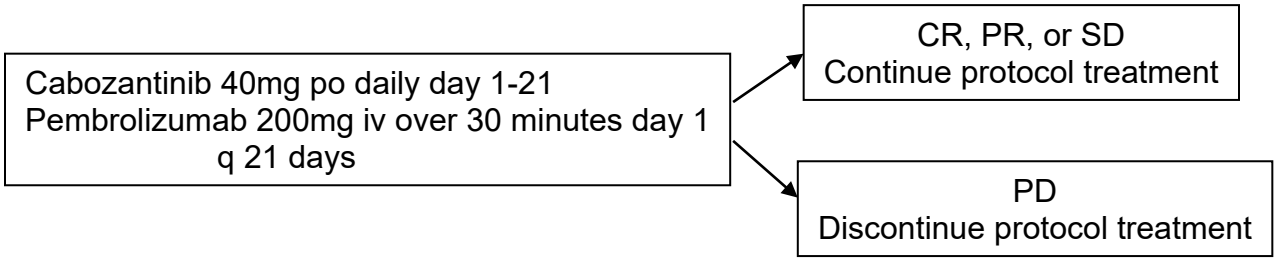
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
GC	Gastroesophageal Adenocarcinoma
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PFS-6	Progression Free Survival at 6 months
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase 2 Study of cabozantinib combined with pembrolizumab in metastatic or recurrent gastric and gastroesophageal Adenocarcinoma (mGC)
Short Title	Cabozantinib and pembrolizumab in 2L+ gastric and gastroesophageal adenocarcinomas
Protocol Number	UCI 18-124
Phase	2
Operational Changes during the COVID-19 Pandemic	For the duration of the COVID-19 pandemic and in response to directives from the Vice Chancellor for Research and the UCI Human Research Protections Program, the Chao Family Comprehensive Cancer Center's Stern Center for Cancer Clinical Trials and Research will be modifying operations as outlined in Interim Standard Operating Procedure "Clinical Trial Enrollment and Operations during the COVID-19 Pandemic" dated 06April2020. In addition, the University of California Irvine Medical Center Pharmacy Services has issued guidance regarding the shipment of Investigational Drug Product directly to clinical trial participants when in-person clinic visits are not feasible or recommended. This new process is described in "Investigational Drug Services: Emergent Shipment of Investigational Product Policy" dated 23March2020. Current versions of these SOP and Policy documents may be obtained at the following URL: \\hs.uci.edu\myshare\Cancer Center Research\COVID-19\Research\SOPs and Guidelines
Methodology	Open label, single arm
Study Duration	3 years
Study Center(s)	Single Center
Objectives	Primary objective: To estimate the efficacy of cabozantinib combined with pembrolizumab in patients with advanced gastric and gastroesophageal adenocarcinoma (GC) Primary Endpoint: 6 months progression-free survival (PFS-6) Secondary Objective: efficacy, safety, Secondary Endpoint: overall survival, objective response rate, adverse events

Number of Subjects	Up to 27 subjects
Diagnosis and Main Inclusion Criteria	• Histologically proven unresectable or recurrent gastric or gastroesophageal adenocarcinoma • At least one prior chemotherapy regimen including a fluoropyrimidine and/or platinum agent • At least one line of treatment with a PD-1 or PD-L1 inhibitor in patients with PD-L1 CPS score >=10% • Age ≥ 18 years • Performance status (Eastern Cooperative Oncology Group) ≤ 2 • Adequate bone marrow function (ANC≥1000/mcL); and platelet count ≥ 60,000/mcL • Adequate liver function (total serum bilirubin level within normal institutional limits (or <3mg/dL in patients with Gilbert's disease) and serum transaminases ≤3xULN or ≤5xULN if liver metastasis is present); • Adequate renal function (serum creatinine level < 1.5xULN) • An expected survival period of>3 months • Patients with known MSI-High or dMMR tumors must have disease progression after at least one line of immunotherapy
Study Product(s), Dose, Route, Regimen	Cabozantinib 40 mg p.o. daily days 1-21 Pembrolizumab 200 mg i.v. day 1 every 21 days
Study Duration	The study will consist of a screening period of up to 28 days, a treatment period (21 day cycles), and a follow up period of up to 18 months after enrollment of the last patient or until death, whichever occurs first. Subjects will be allowed to continue treatment on study until disease progression, unacceptable toxicity or withdrawal of consent.
Statistical Methodology	Main objective is to estimate the efficacy of the combination regimen with PFS-6 as a primary endpoint. The null hypothesis in this heavily pre-treated population is a PFS-6 of 5%. The alternative hypothesis assumes a PFS-6 of 20% or more. A 2-stage approach will be used. If PFS-6 is seen in at least 2 out of the first 19 patients, the cohort will be expanded to a total of 27 patients. If the PFS-6 is achieved in at least 4 patients in the expanded cohort, that would be sufficient evidence to reject the null hypothesis of 5% in favor of the alternative hypothesis of 20% or more.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Gastric cancer is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide[1]. The incidence of GC varies with different geographic regions, with over 70% of GCs occurring in developing countries[2]. Gastric cancer often presents as advanced disease upon diagnosis, comprising approximately 40% of newly diagnosed cases in the United States (US) and Europe, and approximately 20% in Japan and Korea, where early detection is common[2].

Gastric cancer, including GEJ carcinoma, is a heterogeneous disease with several established risk factors, including environmental, genetic, and behavioral risks. There has been a steady decline in GC mortality attributable to dietary and lifestyle changes worldwide and to decreasing infection with Helicobacter pylori, which is considered the main cause of GC/GEJ in Asian countries[3]. However, the incidence of GEJ tumors has increased considerably due to increases in risk factors such as obesity and gastroesophageal reflux disease[1].

Gastroesophageal junction cancer anatomically straddles the distal esophagus and proximal stomach. Due to its anatomic location and given that, like GC, the majority of GEJ tumors are adenocarcinomas, GEJ tumors are frequently grouped together with GC.

Adenocarcinoma is further classified into 2 distinct types: intestinal (well-differentiated) or diffuse (undifferentiated)[4].

Until optimal, tumor-specific treatment strategies are defined, advanced and metastatic GEJ cancer is treated and managed in a similar fashion to GC[5]. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium [S1]) are generally considered as first-line (1L), standard-of-care treatment options in metastatic GC and GEJ cancer across geographic regions[6][7]. These platinum/fluoropyrimidine combinations are also generally accepted as active comparators in Phase 2 or Phase 3 randomized studies by health authorities worldwide[2]. The different biological characteristics and treatment approaches among regions result in different survival outcomes, with median overall survival (mOS) durations of 12 to 14 months in Asian countries and 8 to 11 months in the United States (US) and Europe[6][7].

While these cytotoxic agents are clinically active, with a 30% to 50% objective response rate (ORR) in the 1L GC treatment setting, this clinical activity is accompanied by significant toxicity. Grade 3/4 toxicities up to 77% have been reported for doublet regimens and > 80% for triplet regimens[8][9][10][11]. Hematological toxicity is the major problem; Grade 3/4 neutropenia has been reported in approximately 40% of participants treated with platinum doublets, and has increased to 82% when docetaxel was added on. Renal toxicity and neuropathy are the main reasons for discontinuation of platinum treatment. Gastrointestinal complaints are also common. Additionally, despite ORRs of 30% to 50%, chemotherapy has resulted in few participants achieving complete response (CR).

Since it is increasingly unlikely to induce longterm remission in patients by a first-line treatment only, a potential way forward could be to expand the lines of treatment from the first- to the second-line and beyond[12]. Indeed, currently roughly 50% of patients progressing after firstline maintain acceptable general conditions and are still good candidates to receive further therapies[12]. Also, the benefit of second-line chemotherapy has been convincingly established in randomised trials[13][14][15], and more recently, the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) ramucirumab has been shown to improve survival either as single agent over BSC[16] or combined with paclitaxel over paclitaxel alone in pretreated patients[17].

Monochemotherapy versus BSC

Three are the landmark phase III randomised trials that successfully explored the role of second-line monochemotherapy in patients with GC.

The German Arbeitsgemeinschaft Internistische Onkologie trial compared a 3-week schedule of irinotecan 250 mg/m² (escalated up to 350 mg/m² depending on toxicity) with BSC in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 who had received prior fluoropyrimidine/platinum combination and whose disease progressed during or within 6 months following first line[18]. Although the study was terminated prematurely due to poor accrual, among 40 enrolled patients the median OS was significantly longer in the irinotecan arm than in the BSC arm (4 vs 2.4 months, HR=0.48, p=0.023). The UK COUGAR-2 trial enrolled 168 patients to receive either docetaxel 75 mg/m² every 3 weeks plus BSC for a maximum of six cycles or BSC alone[19]. The median OS was improved with docetaxel compared with BSC (5.2 vs 3.6 months, HR=0.67, p=0.01). Despite a higher incidence of grade 3–4 neutropenia, infection and febrile neutropenia, patients receiving docetaxel experienced less pain, nausea, vomiting and constipation and decreased dysphagia and abdominal pain.

A Korean trial tried to answer the question about the optimal cytotoxics to be used in second line[20]. In this study, 202 patients with ECOG PS 0–1 and failing one or two prior chemotherapy lines were randomised in a 2:1 ratio to either salvage chemotherapy (docetaxel 60 mg/m² every 3 weeks or irinotecan 150 mg/m² every 2 weeks upon investigator's choice) or BSC. The administration of second-line chemotherapy resulted in a significant improvement in OS compared with BSC (5.3 vs 3.8 months, HR=0.657, p=0.007), while no survival difference was recorded between docetaxel and irinotecan (5.2 vs 6.5 months, p=0.116). Even side effects were similar in both treatment arms.

A meta-analysis of patient-level data from the abovementioned trials including a total of 410 patients underscored the median OS gain of roughly 2 months for second-line monochemotherapy as compared with BSC, with a significant reduction in the risk of death by 37% (HR=0.63, p<0.0001). This benefit was conferred by both irinotecan and docetaxel and was of similar magnitude through patients of different ethnic origin[21]. Of note, when we consider these results we have to remember that the docetaxel benefit is limited to a 3-week schedule at a higher dose, while the weekly lower dose regimen did not seem to yield a similar advantage[15].

On the contrary, a weekly paclitaxel regimen provided an OS comparable to that achieved with irinotecan in 219 patients refractory to standard first-line treatment (9.5 vs 8.4 months, HR=1.13, p=0.38)[14].

Combination chemotherapy versus monochemotherapy

Unlike the first-line setting, combination chemotherapy failed to demonstrate a survival benefit over single.-agent in pretreated AGC. In a small Korean phase II trial, irinotecan monotherapy was as effective as FOLFIRI in terms of ORR (17.2% vs 20%, p=0.525), median PFS (2.2 vs 3.0 months, p=0.481) and OS (5.8 vs 6.7 months, p=0.514); grade 3–4 toxicity was also superimposable between treatment arms[13]. In another Japanese phase III study comparing biweekly irinotecan (60 mg/m²) plus cisplatin (30 mg/m²) to biweekly irinotecan alone (150 mg/m²) in 130 patients refractory to S1-based first-line chemotherapy, PFS was significantly prolonged in the combination arm (3.8 vs 2.8 months, HR 0.68, p=0.0398) but OS did not differ[22]. A meta-analysis of 10 randomised trials confirmed that doublet chemotherapy does not significantly improve OS compared with single agent, while resulting in more grade 3–4 myelosuppression, diarrhoea and fatigue, suggesting monochemotherapy as standard of care in this setting[23].

Ramucirumab: single agent and combinatorial approach

In spite of negative results coming from first-line trials, the therapeutic exploitation of angiogenesis turned out to be effective in second line. Ramucirumab, a fully human immunoglobulin IgG1 monoclonal antibody targeting VEGFR-2, has been shown to significantly improve survival in two pivotal international phase III double-blind, placebo-controlled trials. In the REGARD trial, 355 patients whose disease progressed within 4 months of fluoropyrimidine or platinum-containing first-line chemotherapy or within 6 months of completion of adjuvant therapy, and with an ECOG PS of 0–1, were randomised in a 2:1 ratio to either ramucirumab 8 mg/kg or placebo, intravenously every 2 weeks.16 Patients receiving ramucirumab had an improvement in both OS (5.2 vs 3.8 months, HR=0.776, p=0.047) and PFS (2.1 vs 1.3 months, HR=0.48, p<0.0001), with a reduction in the risk of death by 22% compared with placebo[16]. Also, the disease control rate was significantly higher in the experimental arm (49% vs 23%), although objective responses were infrequent with ramucirumab. The survival benefit remained significant after adjusting for main prognostic variables such as PS, tumour location and

peritoneal disease. The efficacy of ramucirumab alone was comparable to that reported in phase III trials of second-line chemotherapy, with a more favourable toxicity profile.

Similarly, in the RAINBOW trial, which is the largest second-line trial in GC, the addition of ramucirumab to weekly paclitaxel significantly prolonged either median OS (9.6 vs 7.4 months, HR=0.807, p=0.017) or PFS (4.4 vs 2.9 months, HR=0.635, p<0.0001) when compared with paclitaxel monotherapy in 665 patients[17]. A decrease in the risk of death by 19% was seen and a significantly greater proportion of patients attained an objective response in the combination group than in the single-agent group (28% vs 16%, p=0.0001). These results are noteworthy especially in the light of poor risk feature of patients enrolled as demonstrated by the rate of peritoneal metastases higher than 40% in both the experimental and control arms. In a preplanned subgroup analysis, Asian patients derived less survival benefit than non-Asian. A dilution effect by poststudy discontinuation treatment as well as difference in pharmacokinetics has been advocated to explain this discrepant outcome. Interestingly, the survival benefit was achieved while maintaining patient quality of life, delaying symptom worsening and functional status deterioration[24]. The toxicity of ramucirumab was tolerable and, as expected, higher in the combination regimen. In the single-agent trial the most common AE was an increased risk of grade 3 or higher hypertension (8% vs 3%), while when combined with paclitaxel, ramucirumab resulted in significantly increased rates of grade 3–4 neutropenia (40.7% vs 18.8%), though this did not translate into higher incidence of febrile neutropenia. Antiangiogenic class side effects such as proteinuria, bleeding and gastrointestinal perforations were mainly infrequent, mild in grade and more commonly noted in the combination arm.

Thirdline and later lines of therapy

Until recently, no randomized trials with cytotoxics were available to show a survival benefit in 3L+ patients with mGAC. The TAGS trial was a global phase 3 study of adult patients with mGC who had received ≥ 2 prior regimens of chemotherapy. Patients were randomized 2:1 to receive FTD/TPI (35 mg/m2 BID on days 1–5 and 8–12 of each 28-day cycle) or placebo, plus best supportive care. Median overall survival was 5·7 months (95% CI 4·8-6·2) in the trifluridine/tipiracil group and 3·6 months (3·1-4·1) in the placebo group (hazard ratio 0·69 [95% CI 0·56-0·85]; one-sided p=0·00029, two-sided p=0·00058)[25].

Immunotherapy Experience with Pembrolizumab

KEYNOTE-059 was a global, open-label, single-arm, multicohort study in patients with 2+ lines of prior treatment[26]. Treatment consisted of pembrolizumab 200mg every 3 weeks. ORR was the primary endpoint and ranged from 6.4% (PD-L1 negative population) to 15.5% (PD-L1 positive population). Median response duration was reported as 16.3 months in patients with PD-L1 positive tumors.

KEYNOTE-061was a global randomized phase 3 trial of single agent pembrolizumab 200mg every 3 weeks vs. standard dose paclitaxel in patients with advanced gastric or gastro-esophageal junction cancer that progressed on first-line chemotherapy with a platinum and fluoropyrimidine[27]. Primary endpoints were overall survival and progression-free survival in patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or higher. Median overall survival was 9·1 months (95% CI 6·2-10·7) with pembrolizumab and 8·3 months (7·6-9·0) with paclitaxel (hazard ratio [HR] 0·82, 95% CI 0·66-1·03; one-sided p=0·0421). Median progression-free survival was 1·5 months (95% CI 1·4-2·0) with pembrolizumab and 4·1 months (3·1-4·2) with paclitaxel (HR 1·27, 95% CI 1·03-1·57). In the total population, grade 3-5 treatment-

related adverse events occurred in 42 (14%) of the 294 patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel. Pembrolizumab reduced the risk of death by 18% vs. paclitaxel in patients with previously treated G/GEJ cancer and PD-L1 CPS ≥1, although this difference was not statistically significant. In post-hoc analysis, the pembrolizumab treatment effect for OS was greater for CPS ≥5 (HR 0.73; 95% CI 0.52-1.03) and ≥10 (HR 0.64; 95% CI 0.41-1.02).

The pivotal Phase 3 KEYNOTE-062 trial[28] evaluated pembrolizumab, as monotherapy and in combination with chemotherapy (cisplatin and either 5-fluorouracil or capecitabine) for the first-line treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. In the monotherapy arm of the study, pembrolizumab met a primary endpoint by demonstrating noninferiority to chemotherapy, the current standard of care, for overall survival (OS) in the entire intention-to-treat (ITT) population of patients whose tumors expressed PD-L1 (Combined Positive Score [CPS] ≥1). In the combination arm of KEYNOTE-062, pembrolizumab plus chemotherapy was not found to be superior for OS (CPS ≥1 or CPS ≥10) or progression-free survival (PFS) (CPS ≥1) compared with chemotherapy alone. The safety profile of pembrolizumab was consistent with that previously observed in gastric cancer.

From the currently available data the clinical benefit rate from immunotherapy with pembrolizumab appears to be dependent on the PD-L1 expression level, but in general between 6%-30%. While the responses were durable, in the intent to treat population the 6-months PFS (6-PFS) was only 14.1% and the median PFS was 2.0 months. Therefore, the majority of patients treated with immunotherapy will eventually experience disease progression. These findings highlight the remaining unmet need for the majority of patients who either are refractory or develop disease progression following treatment with single agent checkpoint inhibitors.

Proposed strategy to overcome resistance to immunotherapy with Cabozantinib

Cabozantinib, a dual MET and VEGFR inhibitor [29], has been safely combined with PD-1 and PD-L1 inhibitors in solid tumors[30][31]. A recently reported study examined the efficacy of cabozantinib in patients with RCC who progressed on immune checkpoint blockade. Overall, cabozantinib showed promising activity with an ORR of 33% and DCR of 79%, with a median TTF of 6.6 months[32]. We hypothesize that cabozantinib, based on preclinical and clinical observations so far, might contribute to overcoming resistance to PD-1 blockade in mGC. The proposed trial would be in line with regards to medical strategy and anticipated trends for treatment of mGC. It is highly likely that in the short to mid-term the frontline treatment for mGC patients will become a combination of doublet fluoropyrimidine/platinum chemotherapy and checkpoint inhibitors (with trastuzumab if Her- 2 positive [NCT03382600, NCT02901301, NCT02872116]). Nevertheless, the majority of these patients are expected to eventually progress, which highlights the future unmet need of 2L+ treatment options after standard doublet+IO failure.

1.2 Study Agent(s) Background and Associated Known Toxicities

Cabozantinib (Cabometyx®) is an orally available multiple tyrosine kinase receptor (Figure 1). In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis,

metastasis, tumor angiogenesis, drug resistance,and maintenance of the tumor microenvironment.

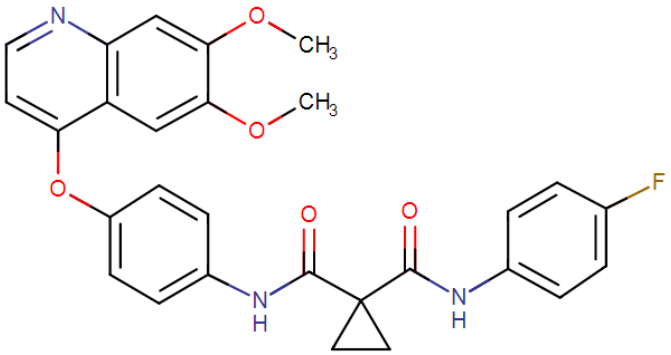


Figure 1 Molecular Structure of Cabozantinib

- **Pharmacodynamics**

  The exposure-response or –safety relationship for cabozantinib is unknown.

  Cardiac Electrophysiology

  The effect of orally administered cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with medullary thyroid cancer administered a dose of 140 mg. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinibtreated patients in this study had a confirmed QTcF > 500 ms nor did any cabozantinib-treated patients in the RCC study (at a dose of 60 mg).

- **Pharmacokinetics**

  Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15.

  Absorption

  Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 3 hours post-dose.

  A 19% increase in the Cmax of the tablet formulation (CABOMETYX) compared to the capsule formulation (COMETRIQ®) was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations.

  Cabozantinib Cmax and AUC values increased by 41% and 57%, respectively, following a highfat meal relative to fasted conditions in healthy subjects administered a single 140 mg oral dose of an investigational cabozantinib capsule formulation.

  Distribution

The oral volume of distribution (Vz/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination

The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steadystate is estimated to be 2.2 L/hr.

Metabolism

Cabozantinib is a substrate of CYP3A4 in vitro.

Excretion

Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational 14C-cabozantinib formulation in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72 hour collection.

Specific Populations

The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (32-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with worse than moderate renal impairment (eGFR less than 29 mL/min/1.73m2) as estimated by MDRD equation or renal impairment requiring dialysis.

Hepatic Impairment
Based on a population pharmacokinetic analysis of cabozantinib in healthy subjects and patients with cancer, no clinically significant differences in the mean cabozantinib exposure were observed between subjects with normal liver function (total bilirubin and AST ≤ ULN) and those with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5x ULN and any AST value). In a dedicated pharmacokinetic study, cabozantinib exposure (AUC0-INF) increased by 63% in patients with moderate hepatic impairment (Child-Pugh B). Patients with severe hepatic impairment have not been studied.

Pediatric Population
The pharmacokinetics of cabozantinib has not been studied in the pediatric population

Drug Interactions

CYP3A4 Inhibition on Cabozantinib
Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC0-inf) by 38%.

CYP3A4 Induction on Cabozantinib

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC0-inf) by 77%.

Cabozantinib on CYP2C8 substrates
No clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) was observed when co-administered with cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) in patients with solid tumors.

Gastric pH modifying agents on Cabozantinib
No clinically-significant effect on plasma cabozantinib exposure (AUC) was observed following co-administration of the proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers.

In vitro Studies

Metabolic Pathways
Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by > 80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

Although cabozantinib is an inhibitor of CYP2C8 in vitro, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this finding, other less sensitive substrates of pathways affected by cabozantinib in vitro (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes in vitro.

Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

Drug Transporter Systems
Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase plasma concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown.

Cabozantinib is a substrate of MRP2 in vitro and MRP2 inhibitors have the potential to increase plasma concentrations of cabozantinib. The clinical relevance of this finding is unknown.

- **Nonclinical Toxicology**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice.

Cabozantinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the in vitro cytogenetic assay using human lymphocytes or in the in vivo mouse micronucleus assay.

Based on nonclinical findings, male and female fertility may be impaired by treatment with CABOMETYX. In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately 13-fold of human AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (5-fold of human AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis.

- **CLINICAL STUDIES**

CELESTIAL
CELESTIAL (NCT01908426) was a phase 3 randomized trial (2:1) of cabozantinib 60mg daily or matching placebo in 707 patients who had received previous treatment with sorafenib, and had disease progression after at least one systemic treatment for hepatocellular carcinoma (up to two lines of previous lines of therapy were allowed)[33]. The primary endpoint, overall survival, was significantly longer with cabozantinib (10.2 months) compared to placebo (8.0 months). Median progression-free survival was also improved (5.2 months vs. 1.9 months). Objective response rate with cabozantinib was reported in 4% of the patients (1% in patients who received placebo). Grade 3 or 4 adverse events occurred in 68% of patients in the cabozantinib group and in 36% in the placebo group. The most common high-grade events were palmar–plantar erythrodysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%), increased aspartate aminotransferase level (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%).

METEOR
METEOR (NCT01865747) was a randomized (1:1), open-label, multicenter study of CABOMETYX versus everolimus conducted in patients with advanced RCC who had received at least 1 prior antiangiogenic therapy. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group.

Patients (N=658) were randomized to receive CABOMETYX (N=330) administered orally at 60 mg daily or everolimus (N=328) administered orally at 10 mg daily. The majority of the patients were male (75%), with a median age of 62 years. Sixty-nine percent (69%) received only one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 46% favorable (0 risk factors), 42% intermediate (1 risk factor), and 13% poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3

or more organs with metastatic disease, including lung (63%),lymph nodes (62%), liver (29%), and bone (22%).

The main efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee among the first 375 subjects randomized. Other efficacy endpoints were objective response rate (ORR) and overall survival (OS) in the Intent-toTreat (ITT) population. Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. Patients received treatment until disease progression or experiencing unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator.

Statistically significant improvements in PFS, OS, and ORR were demonstrated for CABOMETYX compared to everolimus (Figures 2 and 3 and Tables 1 and 2).

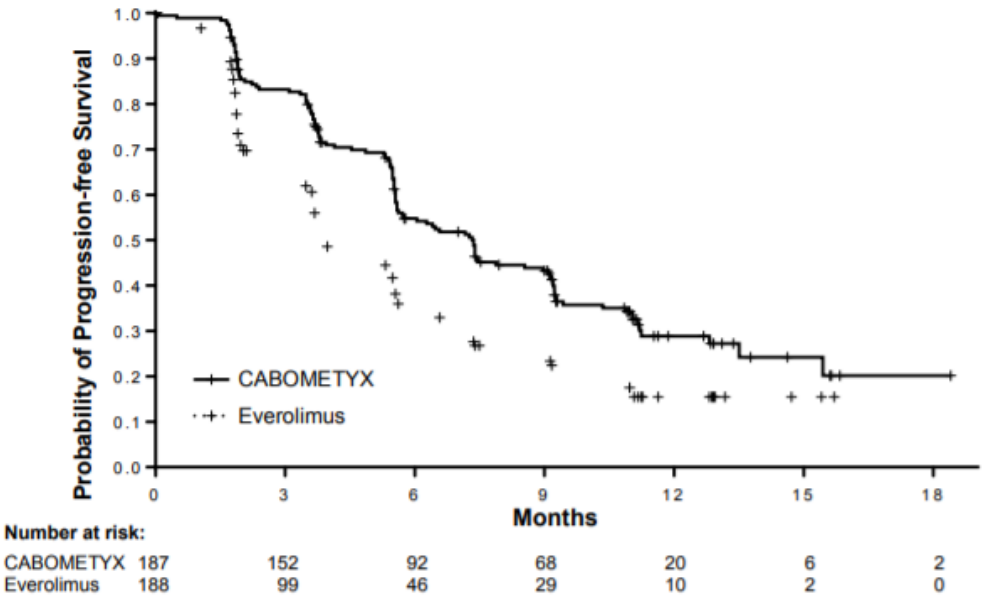


Figure 2: Progression-Free Survival in Study 1 (First 375 Randomized)

Endpoint	CABOMETYX	Everolimus
	N = 187	N = 188
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001	

Table 1: Progression-Free Survival in Study 1 (First 375 Randomized)

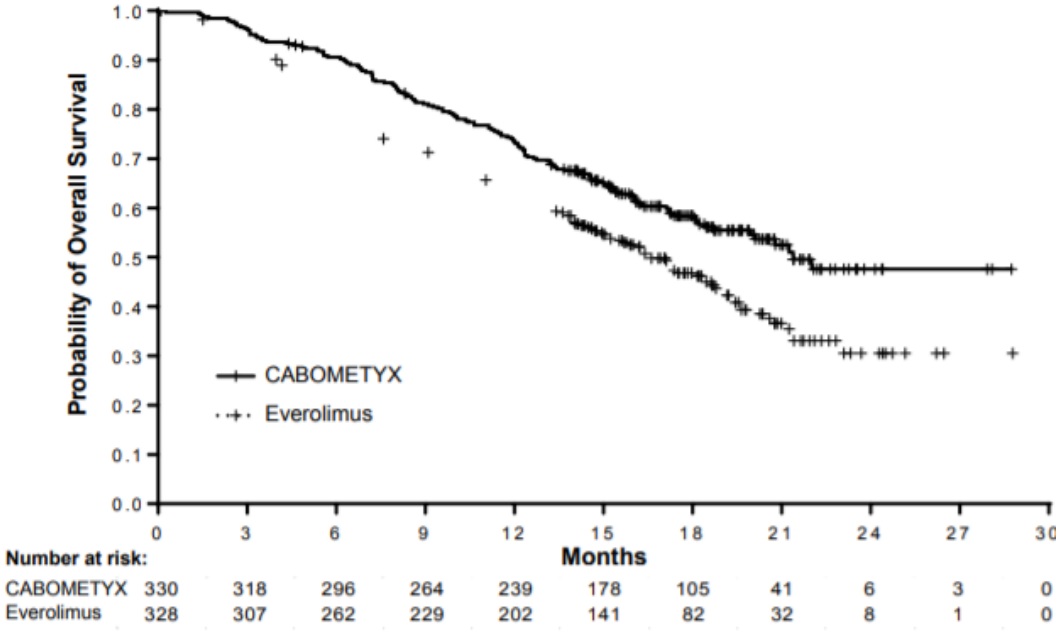


Figure 3: Overall Survival in Study 1 (ITT)

Endpoint	CABOMETYX	Everolimus
	N = 330	N = 328
Median OS (95% CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value[1]	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value[2]	p<0.0001	

Table 2. Overall Survival and Objective Response Rate in Study 1 (ITT)
[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)
[2] chi-squared test

CABOSUN

CABOSUN (NCT01835158) was a randomized (1:1), open-label, multicenter study of CABOMETYX versus sunitinib conducted in patients with advanced RCC who had not received prior therapy. Patients were randomized to receive CABOMETYX (N=79) 60 mg orally daily or sunitinib (N=78) 50 mg orally daily (4 weeks on treatment followed by 2 weeks off) until disease progression or unacceptable toxicity. All patients were required to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no).

The majority of patients were male (78%), with a median age of 63 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor (≥3 risk factors). Thirty-six percent (36%) patients had bone metastases. Forty-six percent (46%) of patients were ECOG 0, 41% ECOG 1, and 13% ECOG 2.

The major efficacy outcome measure was progression-free survival (PFS) by a retrospective blinded independent radiology review committee (BIRC).

A statistically significant improvement in PFS, as assessed by a blinded independent radiology review committee, was demonstrated for CABOMETYX compared to sunitinib (Figure 4, Table 3). The OS results are presented in Figure 5 and Table 3; ORR results are presented in Table 3.

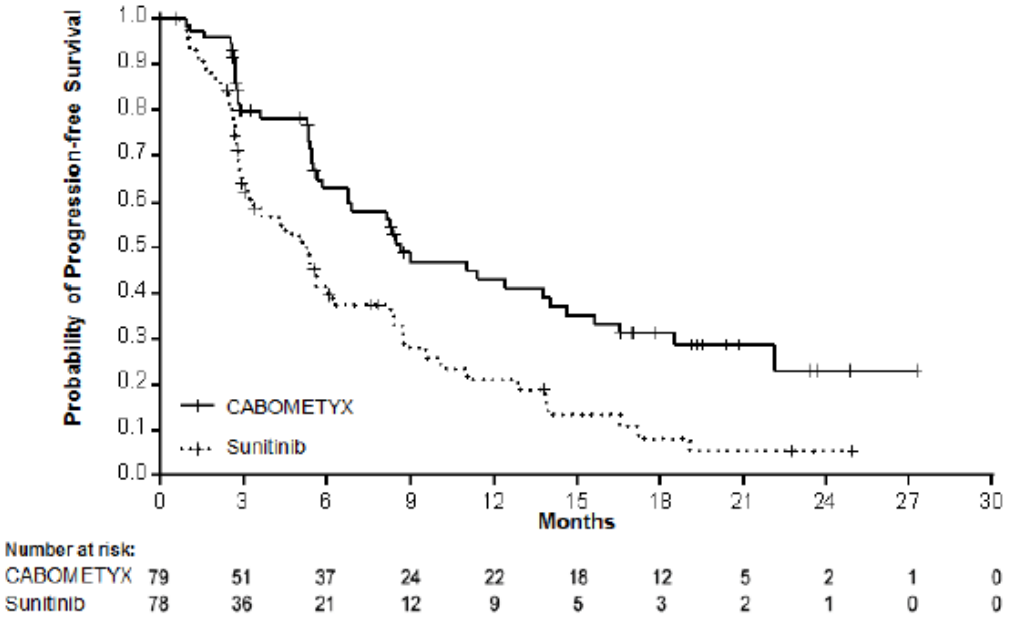


Figure 4: Progression-Free Survival in CABOSUN (ITT)

Endpoint	CABOMETYX	Sunitinib
	N = 79	N = 78
Progression-Free Survival[1]		
Events, n(%)	43 (54)	49 (63)
Median PFS (95% CI), months[1]	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
Hazard Ratio[2] (95% CI), p-value[3]	0.48 (0.31, 0.74), p=0.0008	
Overall Survival		
Events, n(%)	43 (54)	47 (60)
Hazard Ratio[2,4] (95% CI)	0.80 (0.53, 1.21)	
Confirmed ORR, partial responses only (95% CI)[1,4]	20% (12.0, 30.8)	9% (3.7, 17.6)

Table 3. Progression-free Survival, Overall Survival and Objective Response Rate in CABOSUN (ITT)

[1] as assessed by a retrospective blinded independent radiology review committee (BIRC)
[2] estimated from stratified Cox proportional hazards model with stratification factors IMDC risk group and presence of bone metastases and treatment as covariate
[3] two-sided stratified log-rank test with stratification factors IMDC risk group and presence of bone metastases
[4] no multiplicity adjustments were made for overall survival or ORR

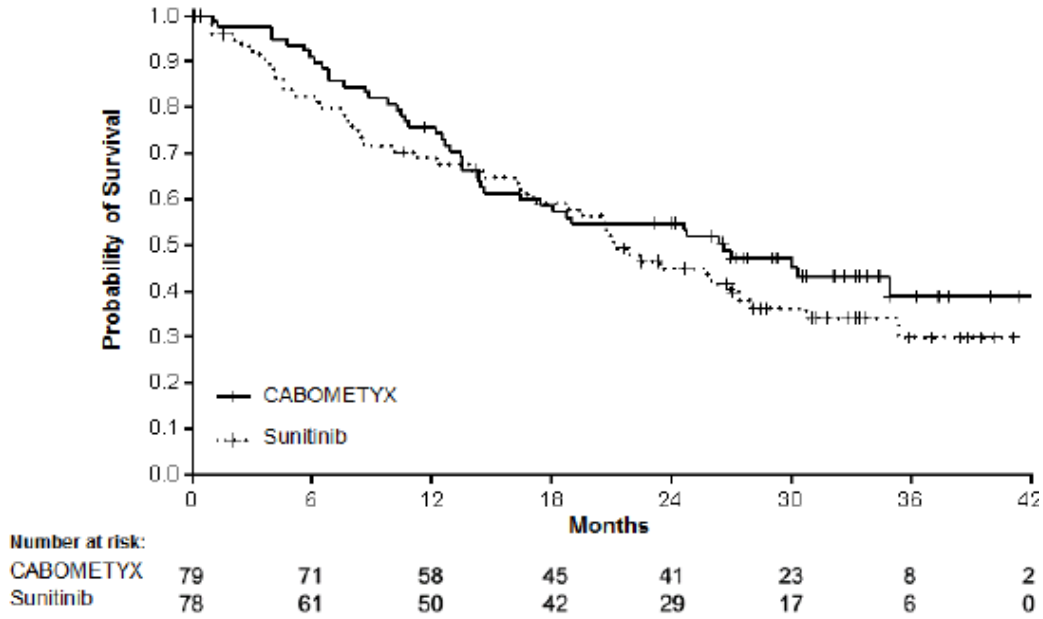


Figure 5: Overall Survival in CABOSUN (ITT)

- **How Supplied / Storage Handling**

  Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 60-mg tablets are oval and the 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 4.

Table 4: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

[a]weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose

- **Cabozantinib Administration**

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

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 4.2 and 4.4 below.

1.3 Other Agents

- **Pembrolizumab [Keytruda®]**

- **Mechanism of Action**

  Pembrolizumab is a highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

- **Intravenous Infusion**

Pembrolizumab DS for IV infusion is produced at several locations to yield: a partially formulated aqueous solution stored under refrigerated (2°C to 8°C) conditions at a concentration of 40.0 to 50.0 mg/mL in 10 millimolar (mM) histidine buffer, pH 5.2 to 5.8; and a fully formulated aqueous solution stored frozen (–40°C°±5°C) at a concentration of 22.5 to 27.5 mg/mL in 10 mM histidine buffer, pH 5.2 to 5.8, containing 7% sucrose and 0.02% polysorbate 80. The drug substance solution from both sources is a clear to opalescent liquid.

The manufacturing process for pembrolizumab is a suspension cell culture process that uses commercially available animal component-free medium. The contents of the production bioreactor are initially filtered to remove intact cells and cell debris, and then 0.2 micron (µm) filtered into presterilized bags.

The purification process for pembrolizumab drug substance consists of chromatography, viral inactivation, viral filtration, ultrafiltration/diafiltration, formulation (only for the fully formulated DS stored frozen), and a final 0.2 µm filtration step.

Two DP dosage forms are available for pembrolizumab for IV infusion: a white to off-white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only. The drug products are manufactured using facilities and practices under GMP requirements.

- **Nonclinical Pharmacology**

Pembrolizumab potently blocks binding to both ligands, PD-L1 and PD-L2, with IC50 values below 1 nM. Pembrolizumab binds to human and Cynomolgus monkey PD-1 with comparable affinity, and blocks the binding of human and Cynomolgus monkey PD-1 to

PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1.

Pembrolizumab enhances T-cell responses in human donor blood cell cultures, with a half-maximal effective concentration of approximately 0.1 to 0.3 nM. Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and Cynomolgus monkeys. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T-cells.

Pembrolizumab does not bind Ig superfamily members CD28, CTLA-4, or ICOS. In in vitro PBMC and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low, and comparable to those induced by trastuzumab. Pembrolizumab does not induce ADCC or CDC.

Safety pharmacology evaluations conducted as part of the 1- and 6-month toxicity and TK studies in Cynomolgus monkeys showed no pembrolizumab–related effects on any parameter evaluated (ECGs, general veterinary and physical examinations with body temperature and blood pressure, clinical observations, and histopathology of tissues from the cardiovascular, respiratory, renal, and nervous systems).

The KDs of pembrolizumab binding to human and Cynomolgus monkey PD-1 were determined by measurement of kinetic rate constants (on/off) in a solid phase format (ForteBio BLI). ForteBio BLI measurements demonstrated that pembrolizumab binds human PD-1 with a fast association rate, dissociates very slowly, and has a high affinity of 29 pM [Table 5].

The ability of pembrolizumab to block the binding of PD-1 ligands, PD-L1 and PD-L2, to human or Cynomolgus monkey PD-1 was measured using a competitive binding assay and detection by fluorometric microvolume assay technology. Pembrolizumab potently blocks binding to both PD-1 ligands with IC50 values below 1 nM [Table 4].

	Kinetic Analysis			**Ligand Blockade**	
	ForteBio Octet (BLI)			**FMAT**	
	k_{assoc}	k_{dissoc}	K_D	PD-L1	PD-L2
Species	1/s	1/Ms	pM	IC_{50} (pM)	IC_{50} (pM)
Human	1.04×10^{6}	3.05×10^{-5}	29	625	695
Cynomolgus	2.05×10^{6}	2.42×10^{-5}	118	712	761
Mouse	no observed binding			N/A	N/A

Table 5 Characterization of Pembrolizumab Binding to PD-1
1/Ms=1 per molar per sec; BLI=biolayer-interferometry; FMAT=fluorometric microvolume assay technology; IC50=half maximal inhibitory concentration; kassoc=association rate constant; KD=dissociation constant; kdissoc=dissociation rate constant; N/A=not applicable; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1; PD-L2=programmed cell death ligand 2; pM=picomolar; s=second.

- **Metabolism**

No traditional metabolism studies were conducted with pembrolizumab per current ICH S6 (R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals.

However, in vivo studies were conducted in C.B17 SCID mice to demonstrate the lack of Fab-arm or half molecule exchange for pembrolizumab. IgG4 wild-type molecules can undergo in vitro and in vivo molecular rearrangement called Fab-arm (or half molecule) exchange by swapping their half molecule with other IgG4 half molecules, thereby generating bispecific or hybrid antibodies [4-3], [4-4]. A point mutation (S228P) in the core hinge region in IgG4 has been shown to be sufficient to prevent the Fab-arm exchange [4-3], [4-4]. The results supported that pembrolizumab, which has a hinge mutation from S to P at Position 228, did not form detectable hybrid antibodies with co-administered wild type IgG4 molecules in vivo in SCID mice (PK007). This observation is consistent with the results of extensive in vitro characterization of pembrolizumab (PK007) and indicates that pembrolizumab is not likely to engage in Fab-arm exchange in humans.

- **Excretion**

No specific studies were performed with pembrolizumab.

- **Toxicology and Toxicokinetics**

All pivotal toxicity studies were conducted in accordance with the principles of GLP. Unless otherwise indicated, all studies were conducted at Merck Research Laboratories, West Point, Pennsylvania, U.S.A. or Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France. The U.S.A. and France are members of the OECD and therefore part of the OECD Mutual Acceptance of Data system. GLP compliance statements are included in all GLP study reports.

- **Specific populations**

The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), renal impairment (eGFR ≥ 15 mL/min/1.73 m2), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. The impact of moderate or severe hepatic impairment on the pharmacokinetics of pembrolizumab is unknown.

Pediatric Patients: Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

- **NONCLINICAL TOXICOLOGY**

- **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

- **Animal Toxicology and/or Pharmacology**

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1

knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

- **CLINICAL STUDIES**

Pembrolizumab has been studied in clinical trials alone or in combination with chemotherapy in a wide range of malignancies. Below the clinical studies pertinent to gastric cancer.

- *Microsatellite Instability-High Cancer*

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST v1.1, and duration of response.

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

Table 6. MSI High Trials.
CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

A total of 149 patients with MSI-H or dMMR cancers were identified across the five trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy. The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Efficacy results are summarized in Tables 7 and 8.

Endpoint	**KEYTRUDA n=149**
Objective Response Rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

Table 7: Efficacy Results for Patients with MSI-H/dMMR Cancer
NR- not reached

	N	**Objective response rate**		**DOR range**
		n (%)	**95% CI**	(months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

Table 8: Response by Tumor Type
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

- *Gastric Cancer*

The efficacy of KEYTRUDA was investigated in KEYNOTE-059 (NCT02335411), a multicenter, nonrandomized, open-label multi-cohort trial that enrolled 259 patients with

gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy. Patients with active autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, as assessed by blinded independent central review, and duration of response.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of ≥ 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 143 patients were: median age 64 years (47% age 65 or older); 77% male; 82% White, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). Eighty-five percent had M1 disease and 7% had M0 disease. Fiftyone percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting.

For the 143 patients, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer.

Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The duration of response ranged from 5.3+ to 14.1+ months.

- *Combination of cabozantinib with pembrolizumab*

The combination of pembrolizumab (Keytruda) and cabozantinib (Cabometyx) has antitumor activity in patients with previously treated metastatic renal cell carcinoma (RCC) and is tolerated at their separate approved doses for this indication, based on the findings from a dose-escalation cohort of a phase I study[34]. Among 8 patients enrolled with RCC of any histology, the best objective response was a partial response in 2 patients and stable disease in 4 patients; 2 patients experienced progressive disease. The maximum-tolerated dose (MTD) was identified as 60 mg of oral cabozantinib daily plus 200 mg of pembrolizumab intravenously every 3 weeks. No dose-limiting toxicities (DLTs) were observed with cabozantinib at 40 mg when used in combination with pembrolizumab in patients evaluable for DLT. One patient required a dose reduction from 60 mg of cabozantinib to 40 mg after cycle 5.

Eligible patients in the phase I study (NCT03149822) had documented RCC of any histology, measurable or evaluable disease based on RECIST v1.1 criteria, adequate organ function, and an ECOG performance status of 0 or 1. Patients received pembrolizumab and cabozantinib in a standard 3+3 dose escalation to determine the DLT, MTD, and objective response rate. Cabozantinib was dosed at 40 mg and 60 mg daily in the first and second cohorts, respectively. Pembrolizumab was dosed at 200 mg every 3 weeks in all cohorts. The original study design included only pretreated patients

but after cabozantinib was approved in the first-line setting in patients with intermediate- and poor-risk disease, the protocol permitted patients with newly diagnosed metastatic RCC.

The DLT assessment window was 21 days; dose-escalation patients who did not complete the DLT assessment window for any reason other than a DLT were considered non-evaluable for DLT and were replaced. Scans were obtained every 9 weeks, and treatment could continue beyond progression. Two patients in the cabozantinib 40-mg cohort were not evaluable for DLT due to nonadherence and were therefore replaced with 3 patients who were treated at the 60-mg dose.
In the first cohort (n = 5), 4 patients had clear cell histology and 1 had non-clear cell RCC; all had prior nephrectomy. The median age was 54 years. Four were intermediate risk and 1 was poor risk by Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria. Three patients in cohort 1 received 1 prior systemic treatment and 2 patients received ≥2. Moreover, 3 patients received prior tyrosine kinase inhibitor (TKI) only and 2 received prior TKI plus immunotherapy.

In cohort 2 (n = 3), the median age of the 3 patients was 47 years. All 3 had clear cell histology, all had prior nephrectomy, and all were MSKCC intermediate risk. Two received 1 prior systemic treatment and 1 received ≥2. Two patients received prior TKI only and 1 received prior TKI and immunotherapy.

Patients in the study were not selected for programmed cell death ligand 1 (PD-L1) expression. No correlation with PD-L1 status and response was seen in tumor samples tested.

1.4 Rationale

Gastric cancer is the third leading cause of cancer mortality and the fifth most common malignancy worldwide[35]. Currently, fluoropyrimidine and platinum-based combinations are the most commonly used first line treatment regimens. Patients who progress after 1st line chemotherapy have few standard treatment options. Paclitaxel and ramucirumab (anti- VEGFR2 mAb) improve OS in 2nd line in metastatic gastric cancer[17]. The phase III ONO-4538-12 (ATTRACTION 2) trial has demonstrated an improved overall survival for nivolumab compared with placebo for patients with heavily pretreated gastric cancer[36]. In the Keynote-59 trial, pembrolizumab produced an ORR of 11.6% in 3L+ mGC, although the response rate was higher (15.5% vs. 6.4%) in patients with PD-L1 positive compared to PD-L1 negative tumors (defined as CPS score of at least 1%)[26]. While the responses were durable, in the intent to treat population the 6-months PFS (6-PFS) was only 14.1% and the median PFS was 2.0 months. These findings highlight the remaining unmet need for the majority of patients who either are refractory or develop disease progression following treatment with single agent checkpoint inhibitors. Cabozantinib has been safely combined with PD-1 and PD-L1 inhibitors in solid tumors[30], [31]. A recently reported study examined the efficacy of cabozantinib in patients with RCC who progressed on immune checkpoint blockade. Overall, cabozantinib showed promising activity with an ORR of 33% and DCR of 79%, with a median TTF of 6.6 months[32]. We hypothesize that cabozantinib, based on preclinical and clinical observations so far, might contribute to overcoming resistance to PD-1 blockade in mGC. The proposed trial would be in line with regards to medical strategy and anticipated trends for treatment of mGC. It is highly likely that in the short to mid-term the frontline treatment for mGC patients will become a combination of doublet fluoropyrimidine/platinum chemotherapy and checkpoint inhibitors (with trastuzumab if Her- 2 positive[NCT03382600, NCT02901301, NCT02872116]). Nevertheless, the

majority of these patients are expected to eventually progress, which highlights the future unmet need of 2L+ treatment options after standard doublet+IO failure.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the efficacy of cabozantinib in combination with pembrolizumab in patients with advanced gastric and gastroesophageal adenocarcinoma who have progressed at least on one line of therapy

2.2 Secondary Objectives

2.2.1 To describe the adverse events associated with cabozantinib in combination with pembrolizumab in patients with advanced gastric and gastroesophageal adenocarcinoma

2.2.2 In patients with measurable disease, to describe any preliminary evidence of anti-tumor activity by assessment of objective response as determined by RECIST v1.1 in patients with advanced gastric and gastroesophageal adenocarcinoma

2.3 Endpoints

The primary endpoint is 6 months progression-free survival (PFS-6).
The secondary endpoints are rates of drug-related grade 3-5 adverse events experienced during and up to four weeks after completion of study treatment. These will be assessed via NCI's CTCAE v5.0 toxicity criteria. Other secondary endpoints are best objective response rate by RECIST v1.1 in patients with measurable disease and overall survival.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed gastric or gastroesophageal adenocarcinoma

3.1.2 Must have locally advanced, recurrent, or metastatic disease not amenable to curative intent surgery.

3.1.3 Must have progressed, or not tolerated, at least one line of treatment with a platinum and/or fluoropyrimidine containing regimen. At least one cycle of combination chemotherapy including a platinum (oxaliplatin, cisplatin, carboplatin) and/or fluoropyrimidine (capecitabine or 5-Fluorouracil) based regimen for advanced disease. Combination regimens with platinum/fluoropyrimidine containing a taxane and or a checkpoint inhibitor are allowed. Patients progressing within six months of perioperative chemotherapy or definitive chemoradiation for localized disease are eligible. Patients who have exhausted all other standard of care options are also eligible.

3.1.4 Must have received and progressed on one previous line of treatment containing a checkpoint inhibitor (if PD-L1 CPS score unknown or ≥ 10%). Patients with PD-

L1 CPS score < 10% are eligible independent of whether they have received previous checkpoint inhibitors.

3.1.5 Age ≥ 18 years.
Because no dosing or adverse event data are currently available on the use of cabozantinib in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.6 Performance status: *ECOG performance status ≤2 (Appendix A).*

3.1.7 Life expectancy of greater than 3 months

3.1.8 Adequate organ and marrow function as defined below:

Leukocytes	≥ 2,000/mcL
absolute neutrophil count	≥ 1000/mcL
platelets	≥ 60,000/mcl
total bilirubin	within normal institutional limits (or <3mg/dL in patients with Gilbert's disease)
AST(SGOT)/ALT(SPGT)	≤ 3 X institutional upper limit of normal or ≤ 5 X if liver metastases are present
creatinine	< 1.5 X upper limit of normal
hemoglobin	≥ 8 g/dL
Serum albumin	≥ 2.8 g/dL
Urine protein/creatinine ration (UPCR)	≤ 1 mg/mg

3.1.9 The effects of cabozantinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 4 months following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.10 Ability to swallow tablets

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

3.1.12 Patients with known MSI-High or dMMR tumors must have disease progression after at least one line of immunotherapy

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy within 2 weeks prior to entering the study

3.2.2 All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to grade 1 or baseline

3.2.3 Patients may not be receiving any other investigational agents.

3.2.4 Patients with known brain metastases or cranial epidural disease unless accurately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. These individuals should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the first dose of study treatment.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, cabozantinib or other agents used in study. Patients with documented previous immune related toxicities which led to discontinuation of a checkpoint inhibitor.

3.2.6 Concomitant anticoagulation with oral anticoagulants (eg, warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitors betrixaban, or platelet inhibitors (eg, clopidogrel).
Allowed anticoagulants are the following:

a. Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
b. Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

3.2.7 The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 x the laboratory ULN within 7 days before the first dose of study treatment.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, the following conditions:

a. ongoing or active infection
b. symptomatic congestive heart failure
c. uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment
d. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism) within 6 months before first dose
e. unstable angina pectoris
f. cardiac arrhythmia

g. evidence of tumor invading GI tract, active peptic ulcer disease, inflammatory inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
h. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.
Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
i. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose.
j. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
k. Lesions invading any major blood vessels.
l. Other clinically significant disorders that would preclude safe study participation:
    i. Serious non-healing wound/ulcer/bone fracture
    ii. Uncompensated/symptomatic hypothyroidism
    iii. Moderate to severe hepatic impairment (Child-Pugh B or C)
m. psychiatric illness/social situations that would limit compliance with study requirements.

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

3.2.10 Prior treatment with cabozantinib

3.2.11 Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment.

$$\text{Corrected QT (QTc)} = QT / \sqrt[3]{RR}$$

QT: duration of QT interval
RR: duration of RR interval

Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 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.

3.2.12 Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment.

3.2.13 History of another primary cancer within the last 3 years with the exception of non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in-situ and not treated with systemic therapy.

3.2.14 Inability to comply with study and follow-up procedures as judged by the Investigator

3.2.15 Patients must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

3.2.16 Has squamous cell or undifferentiated gastric cancer.

3.2.17 Has received prior cytotoxic, biologic or other systemic anticancer therapy including investigational agents within 2 weeks prior to randomization.

3.2.18 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.

3.2.19 Has received a live vaccine within 30 days prior to the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

3.2.20 Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.

3.2.21 Has severe hypersensitivity (Grade ≥ 3) to pembrolizumab or cabozantinib and/or any of their excipients.

3.2.22 Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

3.2.23 Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

3.2.24 Has an active infection requiring systemic therapy.

3.2.25 Has a known history of human immunodeficiency virus (HIV) infection.
Note: No HIV testing is required unless mandated by local health authority.

3.2.26 Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

3.2.27 Has a history or current evidence of any condition (eg, known deficiency of the enzyme dihydropyrimidine dehydrogenase), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

3.3 **Inclusion of Women, Minorities, Vulnerable Populations** Both men and women and members of all races and ethnic groups are eligible for this trial. Non-English speaking, deaf, hard of hearing and illiterate individuals are eligible for this trial.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Patients will be treated with cabozantinib 40 mg p.o. on days 1-21 and pembrolizumab 200 mg i.v. on day 1 every 21 days.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Cabozantinib	None	40 mg daily	At least 1 hour before or at least 2 hours after eating	Days 1-21	3 weeks (21 days)
Pembrolizumab	Supportive care for infusion reactions per institutional guidelines	200 mg in 50 cc NS 0.9% over 30 min	IV	Day 1	

4.1.2 Concomitant Medications

4.1.2.1 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 (e.g., ASCO or ESMO guidelines).
- Bisphosphonates or RANK-L inhibitors 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 (Section 7.1.2). 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. Withhold cabozantinib for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Inhaled, intranasal, intra-articular, and topical corticosteroids are allowed if minimal systemic absorption. Systemic corticosteroids are allowed for control of infusion reactions or irAEs and must be tapered to a dose level ≤ 10 mg/day of prednisone equivalent before next administration of the IO agent. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed.

- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
    - At the time of first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
        - Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 4.1.2.2 for prohibited anticoagulants.
    - After first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
        - Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. See section 7.1.2 for management of thromboembolic complications while on study. See section 4.1.2.2 for prohibited anticoagulants. Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used concomitantly with heparin or factor Xa inhibitors due to the increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines.

4.1.2.2 Prohibited or Restricted Therapy:

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

- Any investigational agent or investigational medical device.
- Oral anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardio-protection per local applicable guidelines), until 4 weeks after cabozantinib has been permanently discontinued.
- Any non-protocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 4.1.2.1.
- Live vaccines are prohibited while on study and until 5 months after last dose of IO agent (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines). The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.
- Metamizole (dipyrone) because of its potential for causing agranulocytosis.

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 (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 (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 (e.g., 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 (e.g., 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.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5.5). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

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

Dose Modification Table

Dose Level	Agent	Dose
1 (starting dose)	Cabozantinib	40 mg
1 (starting dose)	Pembrolizumab	200 mg
-1 (50% reduction)	Cabozantinib	20 mg
-2	Cabozantinib	20 mg every other day

Toxicities:

Toxicity Dose Reductions		
NCI CTC Grade	**Cabozantinib**	**Pembrolizumab**
Grade 0-2	No change from original starting dose	No change from original starting dose (unless described in 4.2.1)
Intolerable grade 2 or grade 3	Hold until resolved to ≤ Grade 1 then resume **to dose level 1 or -1, depending on physician assessment**	Hold until resolved to ≤ Grade 2, then resume **at dose level 1** (unless described in 4.2.1)
Second episode of grade 3 or intolerable grade 2 first episode of grade 4 toxicity	Hold until resolved to ≤ Grade 1 then reduce **to dose level one less than previous (i.e. -1 or -2)** Discontinue permanently (unless investigator determines patient is deriving clear clinical benefit)	Discontinue permanently (unless described in 4.2.1)
Third episode of grade 3	Remove subject from trial	Not applicable

4.3 Pembrolizumab adjustment for toxicity

No dosage reductions of pembrolizumab are recommended; treatment is withheld or discontinued to manage toxicities.

Colitis (immune-mediated):

Grade 2 or 3: Withhold pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper); may resume upon recovery to grade 0 or 1 toxicity after corticosteroid taper.

Grade 4: Permanently discontinue pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Dermatologic toxicity (immune-mediated):

Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN): Withhold pembrolizumab and refer for specialized care for assessment and treatment; may require corticosteroids (based on the severity).

Grade 4 severe skin reactions or confirmed SJS or TEN: Permanently discontinue pembrolizumab and refer for specialized care for assessment and treatment; may require corticosteroids (based on the severity).

Endocrinopathies (immune-mediated):

Grade 3 or 4: Withhold pembrolizumab until clinically stable.

Hyperglycemia, severe: Also administer antihyperglycemics.

Hyperthyroidism, severe (grade 3) or life-threatening (grade 4): Manage with thionamides and beta blockers as appropriate; may resume upon recovery to grade 0 or 1 toxicity or discontinue.

Hypophysitis, grade 2 (symptomatic): Also administer corticosteroids (followed by a taper) and hormone-replacement therapy if appropriate; may resume upon recovery to grade 0 or 1 toxicity or discontinue.

Hypophysitis, grade 3 or 4: Withhold or discontinue pembrolizumab (based on severity); also administer corticosteroids (followed by a taper) and hormone-replacement therapy as clinically indicated.

Nephritis (immune-mediated):

Grade 2: Withhold pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper); may resume upon recovery to grade 0 or 1 toxicity after corticosteroid taper.

Grade 3 or 4: Permanently discontinue pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Pneumonitis (immune-mediated):

Grade 2: Withhold pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper); may resume upon recovery to grade 0 or 1 toxicity after corticosteroid taper.

Grade 3 or 4 or recurrent grade 2: Permanently discontinue pembrolizumab; administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Other immune-mediated toxicities:

Grade 2 or grade 3 (based on the severity and type of reaction): Withhold pembrolizumab; may require corticosteroids (based on severity). Upon improvement to grade 0 or 1, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at grade 0 or 1 following corticosteroid taper. May consider other systemic immunosuppressants if not controlled by corticosteroids (based on limited data).

Grade 3 (based on the severity and type of reaction) or grade 4: Permanently discontinue pembrolizumab; also administer corticosteroids (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Recurrent immune-mediated adverse reactions, grades 3 or 4: Permanently discontinue pembrolizumab; also administer corticosteroids (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Inability to taper corticosteroids: Permanently discontinue pembrolizumab if unable to reduce corticosteroid dose to prednisone <10 mg/day (or equivalent) within 12 weeks after last pembrolizumab dose (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Persistent grade 2 or 3 adverse reaction (excluding endocrinopathy) that does not recover to grade 0 or 1 within 12 weeks after the last pembrolizumab dose: Permanently discontinue pembrolizumab; also administer corticosteroids (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Infusion-related reaction:

Grade 1 or 2: Interrupt infusion or slow the infusion rate.
Grade 3 or 4: Permanently discontinue pembrolizumab.

4.4 Cabozantinib adjustment for toxicity

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea.

Subjects may also experience other medically important but less frequent AEs including arterial thrombotic AEs (e.g., deep vein thrombosis [DVT], pulmonary embolism, transient ischemic attack [TIA], and myocardial infarction [MI], severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

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

Many adverse events may occur early (within the first few weeks) in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.

Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Section 4.2).

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

Gastrocintestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula [37] are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

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. Guidelines for the evaluation and management of diarrhea are shown in Table 9. 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, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

Table 9: Management of Diarrhea Associated with Cabozantinib

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 for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 7.1.3 for further details).

Non-Gastrointestinal Fistula
Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non GI fistula.

Hemorrhage
Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

Thromboembolic events
Refer to section 7.1.2

Hypertension
Table 10 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 10: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency[c]	• Discontinue cabozantinib treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

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. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

Skin and Subcutaneous Tissue Disorders
Wound healing and surgery: Refer to section 7.1.2

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in Table 11.

Table 11: Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

CTCAE v.5.0 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES 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 PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES 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 high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

Osteonecrosis
Refer to section 7.1.2

Proteinuria
Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 12 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).

Table 12: Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment

RCC, renal cell carcinoma; UC, urothelial carcinoma; UPCR, urine protein/creatinine ratio.

Nervous System Disorders
Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

Hepatocellular Toxicity
Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (eg, liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

Cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 x ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib should be interrupted until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate drug-induced liver injury (DILI). Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.

Infections and Infestations
Refer to section 7.1.2

Blood and Lymphatic System 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. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. 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.

Fatigue
Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

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 when not prohibited by a particular protocol.

Corrected QT Prolongation
The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this

study had a QTcF > 500 ms. Review of the larger safety database (~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms, the following actions must be taken:

- 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
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. 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
- Cabozantinib 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 done as clinically indicated. Cabozantinib treatment must be permanently discontinued if either of the following applies:

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

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. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 4.2 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

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

Angioedema
Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

4.5 Concomitant Medications/Treatments

Cabozantinib

Strong CYP3A4 Inhibitors
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit, grapefruit juice, star fruit and Seville oranges which may also increase exposure of cabozantinib.

Strong CYP3A Inducers
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Avoid St. John's Wort which may also decrease exposure of cabozantinib.

Pembrolizumab

Glucocorticoids
Steroids in excess of a daily dose of 10mg prednisone equivalent have to be avoided due to immunosuppressive effects which can counteract the efficacy of pembrolizumab.

Thalidomide Analogues
Pembrolizumab may enhance the adverse/toxic effect of Thalidomide Analogues. Specifically, mortality may be increased when this combination is used for treatment of refractory multiple myeloma. Avoid combination.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression as defined radiographic progression by RECIST v1.1 criteria OR death OR symptomatic progression as clinically determined by the treating physician
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Treatment held for more than 28 days
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow Up

Patients will be followed every 3 months until death or 18 months after the last patient is enrolled, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up after removal from treatment is every 3 months (either clinic visit or phone call).

4.8 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.6 apply. Notify the Principal Investigator via email (fdayyani@hs.uci.edu and uci18124@hs.uci.edu), and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.9 Patient Replacement

Patients will not be replaced

5.0 STUDY PROCEDURES

Telemedicine Visits
In-person visits are the preferred study visit method for collection of the assessments and procedures. Study visits conducted by phone or videoconferencing technology (i.e., “virtual” or “telemedicine” visits), including adverse event assessments for patients, may be substituted for protocol-required in-person visits, if the site investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit.

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained as long as these assessments are completed within 28 days prior to registration.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Screening Confirmation

Patient information should be entered into Oncore within 1 business day of consent. Sites are responsible for assigning subject ID. Sites will be assigned a unique site code. Subject IDs should follow a format with the unique site code followed by the sequential patient ID. For example, Site Code-Sequential Number (i.e. for UCI’s first patient the subject ID will be 01-01). (Refer to Oncore SOP for Oncore data entry instructions)

5.1.3 Medical history

Complete medical, oncology and surgical history, history of infections

5.1.4 Demographics

Age, gender, race, ethnicity

5.1.5 Review subject eligibility criteria

5.1.6 Review previous and concomitant medications

5.1.7 Physical exam

5.1.8 Vital signs

Temperature, pulse respirations, blood pressure, height, and weight (height only at screening)

5.1.9 ECOG Performance status

5.1.10 Hematology

Complete blood count with differential (CBC)

5.1.11 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, hemoglobin, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, TSH, fT3, fT4, total bilirubin, urine protein/creatinine ratio, PT/INR and PTT,.

Tumor Markers (Optional)
Carcinoembryonic antigen (CEA) and cancer-related antigen 19-9 (CA 19-9).

5.1.12 *Urine studies*

Urine dipstick; if ++ or higher, random urine protein and creatinine, urine protein to creatinine ratio

5.1.13 12-lead ECG

5.1.14 Pregnancy test (for females of child bearing potential)

See section 3.1.8.1 for definition.

5.1.15 Tumor assessment

To be performed with computed tomography of the chest with contrast only (if contrast allergy, CT chest may be done without contrast), and abdomen/pelvis with contrast per physician discretion. CT abdomen/pelvis may be replaced with MRI Abdomen/pelvis per clinical judgement of the treating physician. Additional imaging is indicated at baseline if there is clinical suspicion for other organ involvement (e.g.. MRI or CT brain and bone scan).
Imaging is to be performed at baseline within 28 days of starting treatment

5.1.16 Serious Adverse Events Assessment

5.2 Registration Procedures for participating sites only

Prior to confirmation of registration the below items must be emailed via secure email to the initiating site for review and approval.

1. Redacted source documentation required to confirm eligibility (including but not limited to):
    a. Pathology report
    b. Physical exam including ECOG, medical and oncology history
    c. All screening labs
2. Signed eligibility criteria

All items must be emailed via secure email to (fdayyani@hs.uci.edu and uci18124@hs.uci.edu) UCI CFCCC at least 3 business days before planned treatment start date.

Upon receipt of all required documents, UCI CFCCC will provide confirmation of registration. Subjects may not begin study treatment without confirmation of registration.

5.3 Procedures During Treatment

5.3.1 Prior to Each Treatment Cycle

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Adverse events
- Study drug accountability
- Review previous and concomitant medications
- Pregnancy Test (if applicable)

Site must maintain an accurate and timely record of dispensing of study drug to subject, and receipt of all study drug and pill diaries.

5.3.2 Within 30 days after treatment termination

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Adverse events
- Review previous and concomitant medications
- Pregnancy Test (if applicable)

5.3.3 Tumor Assessments

- To be completed every 8 weeks (+/- one week) during first year of treatment and every 3 months (+/- one week) after the first year until patient comes off study

5.4 Follow-up Procedures

Patients will be followed every three months after completion of (or early withdrawal from) study treatment until death or up to 18 months after the last patient is enrolled, whichever comes first.

- Review of systems and determination of live status (either in clinic during standard visit or by phone)

5.5 Time and Events Table

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Baseline -28 to -1 days	C1D1 +/- 3 days	At every cycle (21 days) +/- 3 days	q 8 Weeks for first year, q 3 months after the first year +/- 1 week	Off Treatment	Follow-up (q 3 months until death or up to 18 months after last patient is enrolled, whichever occurs first) +/- 14 days
Assessment						
Informed Consent	X					
History and PE	X	X	X		X	
Concomitant Medications	X	X	X		X	
Performance Status	X	X	X		X	
Adverse Events	X**	X	X		X	
Tumor Measurements	X			X		
CT CAP or CT chest/MRI Abd/Pelvis	X			X		
CBC / CMP / UA / UPCR	X	X	X		X	
PT/INR, PTT	X	X	X***			
TFTs (TSH, free T3, free T4)	X	X	X***			
CEA and CA 19-9 (optional)****			X			
12-lead ECG	X	X	X***		X	
Pregnancy Test*	X	X	X***		X	
Review of systems						X
Study Drug Accountability			X		X	

*Urine or serum pregnancy test is done according to local institutional standard and should be obtained ONLY in women of child-bearing potential.
** Only Serious Adverse Events will be assessed and reported during baseline
*** To be done Day 1 of Weeks 3, 6, 9 and then every 4-6 weeks
**** This is an optional component and should only be collected if done according to local

institutional standards.

5.6 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;

5.5.5 Patient demonstrates disease progression or subject no longer experiences clinical benefit as determined by the investigator (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.6 Patient experiences toxicity, intercurrent illness, or specific conditions in section 4.2 that makes continuation in the protocol unsafe;

5.5.7 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.8 Patient becomes pregnant or patient is breastfeeding (pregnancy to be reported along same timelines as a serious adverse event);

5.5.9 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.10 Sexually active subjects who refuse to use medically accepted barrier methods of contraception during the course of the study and for 4 months after discontinuation of study treatment

5.5.11 Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued

5.5.12 If a subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction of the toxicity and with agreemtn of the investigator

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

5.5.14 Lost to follow-up. If a research subject cannot be located to document survival after 3 attempts including 1 mailed certified letter, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable: All patients receiving cycle 1, day 1 of the protocol treatment.

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

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

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

6.1.2 Disease Parameters

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

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 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 response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques 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. MRI is also acceptable in certain situations (e.g. for body scans). Scans will be done within 28 days prior to cycle 1 and after that every 8 weeks (+/- 7 days) until end of treatment.

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

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

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.

6.1.4.2 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) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of

disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.5 Duration of Response

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

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

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

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression *or death, whichever occurs first.*

Progression is defined as death, radiographic progression as defined in 6.1.4.3, or clinical deterioration attributed to disease progression as judged by the investigator.

6.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

7.0 ADVERSE EVENTS

*Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via AdEERS) reporting **in addition** to routine reporting.*

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

Cabozantinib and pembrolizumab have no known contraindications.

7.1.2 Special Warnings and Precautions for Use

Cabozantinib

Dermatologic toxicity: Palmar-plantar erythrodysesthesia syndrome (PPES) was commonly observed in clinical trials; severe PPES (≥ grade 3) also occurred. May require treatment interruption, dosage reduction, and/or discontinuation.

GI toxicity: Diarrhea was commonly observed in cabozantinib-treated patients in clinical trials. May require therapy interruption and/or dosage reduction. Cabozantinib is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea/vomiting. [US Boxed Warning]: Cometriq: Serious GI perforations and fistulas have been reported when used for medullary thyroid cancer; discontinue for GI perforation or fistula formation. May be fatal. Tracheal/esophageal fistulas were also noted; some cases were fatal. GI fistula/perforation (including fatal perforations) were also reported in patients treated with cabozantinib. Monitor for signs/symptoms of perforations and fistulas, including abscess and sepsis. May require therapy discontinuation.

Hemorrhage: [US Boxed Warning]: Cometriq: Serious and occasionally fatal hemorrhage (including hemoptysis and gastrointestinal) has occurred with cabozantinib when used for medullary thyroid cancer. Monitor for signs/symptoms of bleeding and do not administer to patients with severe hemorrhage or a recent history of hemorrhage or hemoptysis. Severe hemorrhage has also been reported in patients with renal cell cancer and hepatocellular carcinoma, including grade 3 or higher events. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena. Discontinue for grade 3 or 4 hemorrhagic events.

Hypertension: Treatment emergent hypertension was commonly seen in clinical trials (including grade 3 or higher toxicity and hypertensive crisis). Do not initiate cabozantinib in patients with uncontrolled hypertension. Monitor blood pressure prior to therapy initiation and regularly thereafter; withhold for hypertension that is

uncontrolled with appropriate medical management. May require cabozantinib dosage reduction and/or therapy discontinuation.

Infections and infestations: Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g., after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices. Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until complete healing has taken place.

Osteonecrosis of the jaw: Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures. Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis. Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib treatment. Advise subjects regarding oral hygiene practice and to quickly report symptoms to Investigator. Caution should be used in subjects receiving bisphosphonates. Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 3 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time. Withhold cabozantinib for development of ONJ until complete resolution.

Proteinuria: Proteinuria occurred in patients receiving cabozantinib in clinical trials; nephrotic syndrome was also reported (rare). Monitor urine protein regularly and discontinue therapy if nephrotic syndrome develops.

Reversible posterior leukoencephalopathy syndrome: Reversible posterior leukoencephalopathy syndrome (RPLS) has occurred with cabozantinib. Monitor for signs/symptoms of RPLS (seizures, headache, visual disturbances, confusion or altered mental function); if diagnosis confirmed, discontinue therapy.

Thromboembolic events: Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events**.** Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently

discontinued. See Section 4.1.2 for additional restrictions on anticoagulation therapy.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

Wound healing impairment: Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place. Treatment with cabozantinib should be stopped at least 3 weeks prior to elective surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until complete wound healing.

Pembrolizumab

Dermatologic toxicity: Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN, some fatal), exfoliative dermatitis, and bullous pemphigoid may occur with pembrolizumab. Monitor for suspected severe skin reactions and exclude other causes. Based on the severity of the dermatologic toxicity, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Withhold pembrolizumab for signs/symptoms of SJS or TEN and refer for specialized care for assessment and management. Permanently discontinue pembrolizumab if SJS or TEN is confirmed.

Diabetes mellitus: Type 1 diabetes mellitus has occurred (including diabetic ketoacidosis). Monitor closely for hyperglycemia and other signs/symptoms of diabetes. Insulin therapy may be required; if severe hyperglycemia is observed, administer antihyperglycemics and withhold pembrolizumab treatment until glucose control has been accomplished.

Gastrointestinal toxicity: Immune-mediated colitis has occurred, including cases of grade 2 to 4 colitis. The median time to onset of colitis was 3.5 months (range: 10 days to 16.2 months) and the median duration was 1.3 months (range: 1 day to over 8 months). In many patients, colitis was managed with high-dose systemic corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months), followed by a corticosteroid taper. Most patients with colitis experienced resolution. May require treatment interruption, systemic corticosteroid therapy, and/or permanent discontinuation. Monitor for signs and symptoms of colitis; administer systemic corticosteroids for grade 2 or higher colitis.

Hepatotoxicity: Immune-mediated hepatitis occurred (grades 2 to 4 hepatitis). The median onset for hepatitis was 1.3 months (range: 8 days to 21.4 months); the median duration was 1.8 months (range: 8 days to over 20 months). Hepatitis

resolved in most patients. Administer corticosteroids (prednisone 0.5 to 1 mg/kg/day [or equivalent] for grade 2 hepatitis, and prednisone 1 to 2 mg/kg/day [or equivalent] forgrade 3 or higher, each followed by a taper), and withhold or discontinue therapy based on the severity of liver enzyme elevations. Systemic corticosteroids were used to manage immune-mediated hepatitis in many patients; the median duration of high-dose corticosteroid therapy was 5 days (range: 1 to 26 days), followed by a taper. Monitor for liver function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation. Pembrolizumab/axitinib combination therapy may result in higher frequencies of grades 3 and 4 ALT and AST elevations (compared to pembrolizumab monotherapy). The median time to onset of ALT elevation was 2.3 months (range: 7 days to ~20 months) for pembrolizumab/axitinib combination therapy, and over half of patients with ALT elevation required systemic corticosteroids; resolution of grades 2 to 4 ALT elevation occurred in most patients. When rechallenged with either pembrolizumab, axitinib, or both, over half of patients did not experience recurrence of ALT elevation to >3 times ULN. Monitor liver enzymes at baseline and then periodically during treatment; consider more frequent liver enzyme monitoring than for pembrolizumab (or axitinib) monotherapy. If liver enzymes are elevated, withhold pembrolizumab and axitinib, and consider corticosteroids as needed.

Hypersensitivity: Hypersensitivity and anaphylaxis have been observed (rare).

Hypophysitis: Immune-mediated hypophysitis occurred (grades 2, 3, and 4). The median time to onset was 3.7 months (range: 1 day to 12 months) and the median duration was 4.7 months (range: 8 days to over 12 months). Most cases were managed with systemic corticosteroids. Nearly half of patients with hypophysitis experienced resolution. Monitor for signs/symptoms of hypophysitis (eg, hypopituitarism, adrenal insufficiency). May require treatment interruption, systemic corticosteroids and hormone replacement therapy (as clinically indicated), and/or permanent discontinuation.

Infusion-related reactions: Infusion-related reactions (including severe and life-threatening cases) have occurred. Monitor for signs/symptoms of a reaction (eg, rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever). Interrupt infusion and permanently discontinue for severe (grade 3) or life-threatening (grade 4) infusion-related reactions.

Nephrotoxicity: Immune-mediated nephritis has occurred. The onset for autoimmune nephritis was 3.2 to 5.1 months (range: 12 days to 12.8 months) and the median duration was 3.3 months (range: 12 days to over 16 months). Grade 2 or higher nephritis should be managed with systemic corticosteroids (prednisone initial dose of 1 to 2 mg/kg/day [or equivalent], followed by a taper). Most patients required systemic corticosteroids. The median duration of corticosteroid use was 3 to 15 days (range: 1 day to 4 months), followed by a taper. Nephritis resolved in approximately one-third to one-half of affected patients. Monitor for renal function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation.

Pulmonary toxicity: Immune-mediated pneumonitis has been observed, including grade 3, grade 4, and fatal cases. In patients with NSCLC, a higher incidence of pneumonitis was reported in patients who had received prior

thoracic radiation. The median time to development was 3.3 months (range: 2 days to ~19 months) and the median duration was 1.5 months (range: 1 day to over 17 months). Many patients required initial management with high-dose systemic corticosteroids; the median duration of initial corticosteroid therapy was 5 to 8 days (range: 1 day to ~10 months) followed by a corticosteroid taper. Pneumonitis resolved in half of the affected patients. May require treatment interruption, corticosteroid therapy (prednisone 1 to 2 mg/kg /day [or equivalent] followed by a taper, for grade 2 or higher pneumonitis), and/or permanent discontinuation. Monitor for signs and symptoms of pneumonitis; if pneumonitis is suspected, evaluate with radiographic imaging and administer systemic corticosteroids for grade 2 or higher pneumonitis. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation.

Thyroid disorders: Immune-mediated hyperthyroidism, hypothyroidism, and thyroiditis have occurred. The median onset for hyperthyroidism was 1.4 months (range: 1 day to ~22 months) and the median duration was 2.1 months (range: 3 days to over 15 months). Hyperthyroidism resolved in nearly three-fourths of affected patients. Hypothyroidism occurred with a median onset of 3.5 months (range: 1 day to 19 months) and median duration was not reached (range: 2 days to over 27 months). Hypothyroidism resolved in one-fifth of affected patients. The incidence of new or worsening hypothyroidism was higher in patients with squamous cell cancer of the head and neck. Monitor for changes in thyroid function (at baseline, periodically during treatment, and as clinically indicated) and for signs/symptoms of thyroid disorders. Administer thionamides and beta-blockers for hyperthyroidism as appropriate; may require treatment interruption and/or permanent discontinuation. Isolated hypothyroidism may be managed with replacement therapy. Thyroiditis occurred with a median onset of 1.2 months (range 0.5 to 3.5 months).

Other immune-mediated toxicities: Other clinically relevant immune-mediated disorders have been observed (may involve any organ system or tissue, and may be severe or fatal), including rash, exfoliative dermatitis, bullous pemphigoid, uveitis, arthritis, vasculitis, myositis, Guillain-Barré syndrome, pancreatitis, hemolytic anemia, sarcoidosis, serum sickness, myasthenia gravis, myelitis, myocarditis, and encephalitis. While immune-mediated toxicity generally occurs during treatment with pembrolizumab, adverse reactions may also develop after therapy discontinuation. If an immune-mediated adverse event is suspected, evaluate appropriately to confirm or exclude other causes; withhold treatment and administer systemic corticosteroids based on severity of reaction. Upon resolution to grade 0 or 1, initiate corticosteroid taper (continue tapering over at least 1 month). When reaction remains at grade 1 or less during taper may reinitiate pembrolizumab. Immune-mediated adverse reactions that do not resolve with systemic corticosteroids may be managed with other systemic immunosuppressants (based on limited data). Discontinue permanently for severe or grade 3 immune-mediated adverse event that is recurrent or life-threatening.

7.1.3 Interaction with other medications

Cabozantinib

Aprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Bisphosphonate Derivatives: Angiogenesis Inhibitors (Systemic) may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. Risk C: Monitor therapy

Bosentan: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Clofazimine: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk X: Avoid combination

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May decrease the serum concentration of Cabozantinib. Management: Avoid use of strong CYP3A4 inducers with cabozantinib if possible. If combined, cabozantinib dose adjustments are recommended and vary based on the cabozantinib product used and the indication for use. See monograph for details. Risk D: Consider therapy modification

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Cabozantinib. Management: Avoid use of a strong CYP3A4 inhibitor with cabozantinib if possible. If combined, cabozantinib dose adjustments are recommended and vary based on the cabozantinib product used and the indication for use. See monograph for details. Risk D: Consider therapy modification

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification

Duvelisib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. Risk D: Consider therapy modification

Erdafitinib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Erdafitinib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Fosnetupitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk X: Avoid combination

Grapefruit Juice: May increase the serum concentration of Cabozantinib. Risk X: Avoid combination

Idelalisib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk X: Avoid combination

Ivosidenib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Larotrectinib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Lorlatinib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Avoid concurrent use of lorlatinib with any CYP3A4 substrates for which a minimal decrease in serum concentrations of the CYP3A4 substrate could lead to therapeutic failure and serious clinical consequences. Risk D: Consider therapy modification

MiFEPRIStone: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification

Mitotane: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification

MRP2 Inhibitors: May increase the serum concentration of Cabozantinib. Risk C: Monitor therapy

Netupitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Palbociclib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

Pitolisant: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Combined use of pitolisant with a CYP3A4 substrate that has a narrow therapeutic index should be avoided. Other CYP3A4 substrates should be monitored more closely when used with pitolisant. Risk D: Consider therapy modification

Rifabutin: May decrease the serum concentration of Cabozantinib. Risk C: Monitor therapy

Rifapentine: May decrease the serum concentration of Cabozantinib. Risk C: Monitor therapy

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Simeprevir: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Risk C: Monitor therapy

St John's Wort: May decrease the serum concentration of Cabozantinib. Risk X: Avoid combination

Stiripentol: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

Pembrolizumab

Thalidomide Analogues: Pembrolizumab may enhance the adverse/toxic effect of Thalidomide Analogues. Specifically, mortality may be increased when this combination is used for treatment of refractory multiple myeloma. Risk X: Avoid combination.

7.1.4 Adverse Reactions

Cabozantinib

>10%:

Cardiovascular: Hypertension (30% to 61%)

Central nervous system: Fatigue (41% to 56%), mouth pain (36%), voice disorder (19%), headache (11% to 18%), dizziness (11% to 14%)

Dermatologic: Palmar-plantar erythrodysesthesia (42% to 50%), hair discoloration (34%), skin rash (19% to 23%), xeroderma (11% to 19%), alopecia (16%), erythema (11%)

Endocrine & metabolic: Increased lactate dehydrogenase (84%), increased serum triglycerides (53%), hypocalcemia (8% to 52%), hypoalbuminemia (36% to 51%), hypophosphatemia (25% to 48%), weight loss (17% to 48%), hyperglycemia (37%), hypomagnesemia (19%

to 31%), hyponatremia (10% to 30%), increased gamma-glutamyl transferase (27%), hypokalemia (18% to 23%), hypothyroidism (8% to 21%)

Gastrointestinal: Diarrhea (54% to 74%), stomatitis (13% to 51%; grades 3/4: 2% to 5%), nausea (31% to 50%), decreased appetite (46% to 48%), dysgeusia (12% to 34%), vomiting (24% to 32%), constipation (25% to 27%), abdominal pain (23% to 27%), mucositis (14% to 19%), increased serum amylase (16%), dysphagia (13%), dyspepsia (10% to 12%)

Genitourinary: Proteinuria (2% to 12%)

Hematologic & oncologic: Lymphocytopenia (25% to 53%; grades 3/4: 1% to 16%), neutropenia (31% to 43%; 35%; grades 3/4: 2% to 7%), leukopenia (35%), thrombocytopenia (25% to 35%; grades 3/4: 1%), anemia (17% to 31%; grades 3/4: 1% to 5%)

Hepatic: Increased serum aspartate aminotransferase (73% to 86%), increased serum alanine aminotransferase (68% to 86%), increased serum alkaline phosphatase (35% to 52%), hyperbilirubinemia (25%)

Neuromuscular & skeletal: Asthenia (19% to 22%), arthralgia (11% to 14%), limb pain (9% to 14%), muscle spasm (8% to 13%)

Renal: Increased serum creatinine (58%)

Respiratory: Dyspnea (12% to 19%), cough (18%)

1% to 10%:

Cardiovascular: Hypotension (7%), venous thromboembolism (6% to 7%), syncope (grades 3/4: 5%), pulmonary embolism (4%), arterial thromboembolism (1% to 2%), vascular disease (grades 3/4: 1%)

Central nervous system: Anxiety (9%), paresthesia (7%), peripheral sensory neuropathy (7%), pain (grades 3/4: 5%), peripheral neuropathy (5%), depression (grades 3/4: 4%), confusion (grades 3/4: 1%)

Dermatologic: Hyperkeratosis (7%), dermal ulcer (grades 3/4: 3%)

Endocrine & metabolic: Dehydration (7%), hyperkalemia (grades 3/4: 1%)

Gastrointestinal: Hemorrhoids (9%), gastrointestinal hemorrhage (3%), gastrointestinal perforation (1% to 3%), gastrointestinal fistula (1%)

Hematologic & oncologic: Increased hemoglobin (8%), hemorrhage (grade ≥3: 5%)

Neuromuscular & skeletal: Musculoskeletal chest pain (9%), back pain (grades 3/4: 4%), ostealgia (grades 3/4: 3%), osteonecrosis of the jaw (≤1%)

Renal: Acute renal failure (grades 3/4: 4%)

Respiratory: Pulmonary infection (grades 3/4: 4%)

Miscellaneous: Fistula (nongastrointestinal: 4%; includes tracheal/esophageal), wound healing impairment (≤2%)

<1%, postmarketing, and/or case reports: Cholestatic hepatitis, hypertensive crisis, nephrotic syndrome, pancreatitis, reversible posterior leukoencephalopathy syndrome, seizure

Pembrolizumab

>10%:

Cardiovascular: Peripheral edema (14% to 15%), cardiac arrhythmia (11%)

Central nervous system: Fatigue (23% to 43%), pain (22%), headache (11% to 14%)

Dermatologic: Pruritus (11% to 28%), skin rash (13% to 24%), vitiligo (13%)

Endocrine & metabolic: Hyperglycemia (19% to 49%), hypoalbuminemia (27% to 44%), hypertriglyceridemia (33% to 43%), hyponatremia (10% to 38%), hypophosphatemia (19% to 29%), hypocalcemia (15% to 27%), decreased serum bicarbonate (22%), hypercholesterolemia (20%), hypokalemia (15% to 20%), hypoglycemia (13% to 19%), hypothyroidism (9% to 15%), hypercalcemia (14%), hyperkalemia (13%), weight loss (10% to 11%)

Gastrointestinal: Diarrhea (13% to 28%), decreased appetite (16% to 25%), constipation (14% to 22%), abdominal pain (13% to 22%), nausea (11% to 22%), vomiting (12% to 19%)

Genitourinary: Urinary tract infection (15% to 19%), hematuria (12% to 13%)

Hematologic & oncologic: Anemia (17% to 54%; grades 3/4: 4% to 24%), lymphocytopenia (24% to 47%; grades 3/4: 1% to 18%), leukopenia (35%; grades 3/4: 9%), neutropenia (24% to 30%; grades 3/4: 7% to 11%), thrombocytopenia (27%; grades 3/4: 4%), hemorrhage (19%; grades 3/4: 5%), increased INR (19%), prolonged partial thromboplastin time (14%)

Hepatic: Increased serum alkaline phosphatase (17% to 42%), increased serum transaminases (27% to 34%), increased serum aspartate aminotransferase (20% to 34%), increased serum alanine aminotransferase (9% to 27%), increased liver enzymes (13%)

Immunologic: Graft versus host disease (followed by allogeneic hematopoietic stem cell transplantation: 26%)

Infection: Infection (16%)

Neuromuscular & skeletal: Musculoskeletal pain (21% to 32%), arthralgia (10% to 18%), back pain (11% to 12%), asthenia (10% to 11%)

Renal: Increased serum creatinine (11% to 35%)

Respiratory: Upper respiratory tract infection (13% to 28%), cough (14% to 26%), dyspnea (10% to 23%), flu-like symptoms (11%)

Miscellaneous: Fever (11% to 28%)

1% to 10%:

Cardiovascular: Facial edema (10%), pericarditis (4%), pericardial effusion (2%)

Central nervous system: Peripheral neuropathy (2% to 10%)

Endocrine & metabolic: Hyperthyroidism (3% to 10%), thyroiditis (≤2%)

Gastrointestinal: Colitis (2%)

Hepatic: Hyperbilirubinemia (10%), hepatic sinusoidal obstruction syndrome (followed by allogeneic hematopoietic stem cell transplantation: 9%), ascites (grades 3/4: 8%), hepatitis (≤3%)

Immunologic: Antibody development (2%; neutralizing: <1%)

Neuromuscular & skeletal: Arthritis (2%), myositis (≤1%)

Ophthalmic: Uveitis (≤1%)

Renal: Acute renal failure (2%)

Respiratory: Pneumonitis (2% to 3%)

Miscellaneous: Infusion-related reaction (≤9%)

Frequency not defined:

Cardiovascular: Cardiac failure, cardiac tamponade, edema, myocardial infarction, septic shock

Central nervous system: Confusion, polyneuropathy

Dermatologic: Maculopapular rash

Infection: Herpes zoster

Respiratory: Pleural effusion, pneumonia, respiratory failure

Miscellaneous: Fistula, physical health deterioration

<1%, postmarketing, and/or case reports: Anaphylaxis, chronic inflammatory demyelinating polyradiculoneuropathy (Maleissye 2016), diabetic ketoacidosis, encephalitis, Guillain-Barré syndrome, hemolytic anemia, hypersensitivity reaction, hypophysitis, myasthenia gravis, myelitis, myocarditis, nephritis, organ transplant rejection (solid), pancreatitis, sarcoidosis, type 1 diabetes mellitus, vasculitis

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.3 Definitions

7.3.1 Event Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as *any expected or unexpected adverse event* that result in any of the following outcomes:

- Death

- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation- a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

7.3.2 Characteristics and Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

- ***Expectedness": AEs can be 'Unexpected'*** *or 'Expected'*
  -Unexpected: (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents, such as the protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- ***Attribution*** *of the AE:*
  - *Related – The AE is clearly related to the study treatment.*
  - *Not Related – The AE is clearly NOT related to the study treatment.*

7.3.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.3.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

Following events do not satisy criteria for SAE:
Hospitalizations for preplanned procedures
Hospitalization for study-related treatment and procedures

7.3.3.4 Results in persistent or significant disability or incapacity.

7.3.3.5 Is a congenital anomaly/birth defect

7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Reporting Requirements

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore, and must also be reported to the following entities according to the timelines mentioned in the chart below. Serious adverse events collection will start at the time patient signs consent until 30 days after the end of treatment. Adverse events will be collected from the time the research patient begins treatment until 30 days after the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Type	Coordinating Center/Medical Monitor	UCI IRB	Exelixis, Inc.	CFCCC DSMB
Unanticipated Problem	Within 24 hours from date the site is aware of the event, the site should enter this information into OnCore. An email notification should also be sent via email to fdayyani@hs.uci.edu and uci18124@hs.uci.edu.	Within 5 business days submit an Unanticipated Problem Report (UP). Current policy can be found here.	Within 1 business day of learning of the event. Submit a MedWatch Form to Exelixis via fax (650-837-7392) or email (drugsafety@exelixis.com). All follow up information must be sent to Exelixis within 1 business day of PI's receipt of new information. Please refer to section 7.6 for further information.	Within 5 days from date PI is aware of the event. This information must be reported into OnCore.
AEs and SAEs (non-Unanticipated Problem)	Please refer to section 7.5 for reporting timeframes on AEs and SAEs	N/A	Please refer to section 7.6 for other reportable events	Please refer to section 7.5 for clarification on reporting timeframes for AEs and SAEs
Non-compliance	N/A	N/A	N/A	Please refer to section 7.5 for reportable deviations/violations
Serious or continuing non-compliance	Within 24 hours via email to fdayyani@hs.uci.edu and uci18124@hs.uci.edu	Within 5 business days submit a New Information Report	N/A	Within 5 days from date PI is aware of the event.
Prospective/Planned Deviations	At least 5 business days prior to the event via email to fdayyani@hs.uci.edu and uci18124@hs.uci.edu for approval.	At least 48 hours prior to date the request is needed by. Submit a Prospective Deviation Request form	N/A	At the time of progress review as aggregate reports

7.5 Additional Reporting of Events to the CFCCC DSMB and Sponsor Investigator

Adverse Event/ Serious Adverse Events

Event Type	Reporting Timeframe to CFCCC DMSB (Notification is done by entering this information into OnCore within the timelines below)	Reporting Timeframe to Coordinating Center (Notification is done via email to fdayyani@hs.uci.edu and uci18124@hs.uci.edu within the timelines below)
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event	24 hours from date the site is aware of the event.
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event	24 hours from date the site is aware of the event.
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review.	5 business days from the date the site is aware of the event
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*		

Deviations/Violations

Event Type	Reporting Timeframe to CFCCC DSMB (Notification is done by entering this information into OnCore within the timelines below)	Reporting Timeframe to Coordinating Center (Or other entity monitoring/coordinating the trial)
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points).	5 business days from the date the PI is aware of the event	24 hours from the date the site is aware of the event
Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review	5 business days from the date the site is aware of the event

7.6 Other Reporting Requirements to Exelixis

- Pregnancy/Lactation Exposure
  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.

- Medication Errors/Overdose
  Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

8.0 DRUG INFORMATION

8.1 Cabozantinib

A list of the adverse events and potential risks associated with cabozantinib can be found in Section 7.1.

- Other names for the drug(s):
  CABOMETYX
  COMETRIQ

- Classification - type of agent:
  Antineoplastic Agent, Tyrosine Kinase Inhibitor;
  Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor

- Mode of action:
  Cabozantinib is a potent inhibitor of proinvasive receptor tyrosine kinases (RTKs), including AXL, FLT-3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, TYRO3, and VEGFR-1, -2, and -3; induces apoptosis of cancer cells and suppresses tumor growth, metastasis, and angiogenesis

- Storage and stability:
  Store CABOMETYX at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F)

- Protocol dose:
  40 mg daily continuous

- Preparation:
  N/A

- Route of administration for this study:
  Oral

- Incompatibilities:
  None

- Availability:
  Provided by supporter

- Agent Ordering
  Exelixis
  Sub-site(s) will order agent through Exelixis and will receive the agent will ship directly to the sites.

- Side effects:
  The most commonly reported (≥ 25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, palmar-plantar erythrodysesthesia (PPE), weight decreased, vomiting, dysgeusia, and stomatitis.

- **Agent Accountability**

  Accountability for the study drug at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

  The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the study center, use by each patient, and destruction.

  These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Exelixis.

  Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

  Patients will receive instructions for home administration of cabozantinib according to the regimen description above. Cabozantinib is to be taken 1 hour before or 2 hours after meals. If doses of cabozantinib are missed or held, the patient should not make up for the missed doses.

  Patients will be given a study medication diary to complete at home for cabozantinib. Compliance with the dosing regimen will be assessed based on completion of the drug diary and return of unused drug (or empty bottles).

  IMP Destruction
  IMP will be destroyed by the sponsor according to their SOPs. Destruction logs should be made available to Exelixis at the end of the study.
  IMP Returns
  Exelixis will not accept returned IMP

8.2 Pembrolizumab

A list of the adverse events and potential risks associated with Irinotecan can be found in Section 7.1.

- Other names for the drug(s):
  KEYTRUDA

- Classification - type of agent:
  Antineoplastic Agent, Anti-PD-1 Monoclonal Antibody;
  Antineoplastic Agent, Immune Checkpoint Inhibitor;
  Antineoplastic Agent, Monoclonal Antibody

- Mode of action:
  Pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody which inhibits

programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling[38]. Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses.

- Storage and stability:
  - KEYTRUDA for injection (white to off-white lyophilized powder): Carton containing one 50 mg single-dose vial (NDC 0006-3029-02) Store vials under refrigeration at 2°C to 8°C (36°F to 46°F)..
  - KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution): Carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02) Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials (NDC 0006-3026-04) Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
- Protocol dose:
  200 mg on day 1 every 21 days
- Preparation:
  Dilute in 50mL 0.9% Sodium Chloride IVPB
- Route of administration for this study:
  Intravenous infusion
- Incompatibilities:
  None
- Availability:
  Commercially available
- Agent Ordering
  Provided locally by the trial site
- Side effects:
  Most common adverse reactions (reported in ≥20% of patients) were:
  KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is a single-arm, open label, phase-II trial designed as a pilot to see if the treatment regimen is worthy of further study. Specifically, the trial is designed as the first stage of a Simon two-stage, minimax design[39]. The goal is to gather evidence on efficacy or futility of the study treatment in this study population, while monitoring toxicity. The two-stage approach offers economy and exposes the fewest possible participants to potential harm without substantial benefit, with control of the probability of errors in decisions.

Primary Endpoint: For efficacy the primary endpoint is progression-free survival at six months (PFS-6), dating from the first dose of study treatment. Progression is defined and determined as given in Section 61.6. For toxicity, the primary endpoint is the number of participants showing serious toxicity during their participation in the trial. Serious toxicities are given in Section 7.0.

Efficacy Null Hypothesis: Based on current outcomes for this study population[25][26], the null hypothesis is that 5% of evaluable patients will be progression-free at six months.

Efficacy Alternative Hypothesis: Based on our clinical judgment and aspirations, we anticipate that 20% (or more) of evaluable participants will be progression-free at six months. In our view, 20% progression-free at six months is the smallest advance that would be judged clinically worthwhile.

Secondary endpoints:

- Overall survival, defined as time from starting treatment to death from any cause.
- Objective response rate in patients with measurable disease as defined in section 6.0
- Safety as described in the adverse events in section 7.0

9.2 Sample Size and Accrual

Sample Size: Given null- and alternative-hypothesis proportions of 0.05 and 0.20, respectively, approximately 20 evaluable subjects will signal futility/efficacy with 80-percent power and five percent risk of type-I error. Under these conditions the table below gives the number of evaluable subjects required, the smallest number of patients progression-free at six months to signal efficacy, and the probability of correctly declaring futility.

Design Approach	Sample Size	Responses Signal Efficacy	Probability Correctly Asserting Futility
Minimax	19	>=2	0.75

As may be seen, the minimax approach requires 19 evaluable subjects for this project. If at least two participants are progression-free at six months, then the treatment regimen is considered worthy of further study. Given that result, then, in a separate study to complete stage two of the design, an additional eight evaluable subjects would be run. If at least four of the total of 27 evaluable were progression-free at six months that would be sufficient evidence to reject the null hypothesis of five percent in favor of the alternative hypothesis of 20 percent. The probability of declaring futility when in fact the null hypothesis (viz., 5%) is true is at least 75 percent.

No more than nine patients with PD-L1 CPS = 1-9% who are immunotherapy naïve will be enrolled.

Continuous Monitoring for Excess Toxicity: All participants in trial are monitored for serious toxicity for the duration of their participation in the study. Serious toxicities are given in Section 7. A sequential Pocock-type boundary will inform decisions to continue or stop accrual for excess toxicity, as accrual proceeds (Ivanova, 2005). The table below shows the cumulative number of participants enrolled and the corresponding cumulative number of serious toxicities that will signal the underlying risk of serious toxicity exceeds 33 percent (5% risk of type-1 error).

Threshold Number of Cumulative Toxicities that Signal Excess Toxicity as a Function of Cumulative Number Enrolled*

Cumulative Number Enrolled	***Threshold Number Showing Serious Toxicity to Stop Accrual***
1	**-**
2	**-**
3	**-**

4	***4***
5	***5***
6	***5***
7	***6***
8	***7***
9	***7***
10	***7***
11	***8***
12	***8***
13	***9***
14	***9***
15	***10***
16	***10***
17	***11***
18	***11***
19	***12***
20	***12***

* Pocock –type boundary with maximum acceptable probability of toxicity set to 33 percent and type-1 risk of five percent[40].

9.3 Data Analyses Plans

The primary endpoint (PFS-6) will be calculated at 6 months after the last patient enrolled has started treatment, or at the time of progression of the last patient enrolled, whichever occurs first.

Participants will be characterized on host and demographic factors, with continuous measures given as means or medians and categorical measures given as percents. Consistent with the phase-II nature of the research, we will examine the data in many ways to illuminate future research priorities. We will estimate survival curves for progression-free and overall survival, and attempt to identify systematic differences between those who respond to treatment and those who do not. Survival will be estimated by Kaplan-Meier methods. If assumptions are met, we will model survival using Cox proportional- hazards, eliminating ties by subtracting a small, randomly generated amount from the observed times[41]. As may be indicated, we will transform data to correspond better to analytic requirements, using logit transforms for percent data[42] and log or some other approach for continuous measures. As the goals of these secondary analyses are to inform decisions about future research, no formal statistical hypothesis-testing will be done, probabilities from statistical tests will augment clinical judgment in interpretation, and we will not regard overall, study-wise, error rates for these secondary analyses.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by their own institution's COI committee. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the

relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to UCI CFCCC.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosure statements for the PI and participating investigators, as necessary
- A copy of the IRB-approved consent form and HIPAA form
- IRB member list with their occupations and institutional affiliations or a general assurance number will be acceptable.
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Signed protocol signature page

10.4 Data Completion

10.4.1 OnCore Date Entry

Data, as indicated by Sponsor, will be entered into OnCore – UC Irvine's Clinical Trial Management system. The Investigator is responsible for ensuring all entries are accurate and correct. The Investigator must maintain accurate source data that support OnCore data entry. All data will be entered as per Sponsor's specification and timeframe.

10.4.2 Recording of Events

All investigator initiated treatment trials require that adverse events, serious adverse events, deviations, and unanticipated problems be entered into the clinical trial management system (CTMS), OnCore. All entries must be entered in OnCore within the timelines specified in sections 7.5-7.6 of being aware of the adverse event, serious adverse event, violation, deviation, or unanticipated problem. Adverse events and violations/deviations and adverse events that are unanticipated problems that require prompt reporting to the DSMB must be entered into OnCore according to the timelines as specified in section 7.4-7.6.

10.5 Data Management and Monitoring/Auditing

10.5.1 Quality Assurance

Quality assurance activities will be conducted as per UC Irvine Chao Family Comprehensive Cancer Center's Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC Data and Safety Monitoring Board in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site by the Quality Assurance

Officer. Participating sites may follow their own internal quality assurance policies in order to maintain patient safety and data integrity oversight. The investigator must permit study-related monitoring/auditing and provide access to study-related materials.

10.5.2 Data and Safety Monitoring Plan

This is a **risk level 2 study**, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is a study in which the IND is exempt by the FDA.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to Section 7.4 and Section 7.5.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Due to restrictions instituted during the COVID-19 pandemic, planned clinic visits may be performed via telemedicine at the discretion of the Principal Investigator, following the guidelines established in the CFCCC Standard Operating procedure “Interim Standard Operating Procedure: Clinical Trial Enrollment and Operations during the COVID-19 Pandemic” (URL: \\hs.uci.edu\myshare\Cancer Center Research\COVID-19\Research\SOPs and Guidelines). Whenever possible, on-site clinic visits will be replaced by telemedicine visits between the clinic staff and on-study patients.

Emergency Modifications may be enacted if needed to ensure the safety, and well-being of the study patients. Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

All other planned deviations or violations from the protocol must have prior approval by the Principal Investigator and the IRB. Please refer to Section 7.4 for more information on how protocol deviations and violations are defined. It will also provide instructions on when and who to contact and obtain approval from for prospective deviations. Protocol deviations should also be reported in accordance with UCI IRB, UCI CFCCC Stern Center policies and the participating site’s IRB policies.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.10 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.

10.11 Conditions for Terminating the Study

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.

11.0 REFERENCES

[1] *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0.* .

[2] P. Bertuccio *et al.*, "Recent patterns in gastric cancer: A global overview," *Int. J. Cancer*, vol. 125, no. 3, pp. 666–673, Aug. 2009.

[3] P. Lichtenstein *et al.*, "Environmental and Heritable Factors in the Causation of Cancer — Analyses of Cohorts of Twins from Sweden, Denmark, and Finland," *N. Engl. J. Med.*, vol. 343, no. 2, pp. 78–85, Jul. 2000.

[4] P. LAUREN, "THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION.," *Acta*

Pathol. Microbiol. Scand., vol. 64, pp. 31–49, 1965.
[5] S. Hasegawa and T. Yoshikawa, “Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies.,” *Gastric Cancer*, vol. 13, no. 2, pp. 63–73, Jun. 2010.
[6] T. Waddell, M. Verheij, W. Allum, D. Cunningham, A. Cervantes, and D. Arnold, “Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up,” *Ann. Oncol.*, vol. 24, no. suppl 6, pp. vi57–vi63, Oct. 2013.
[7] Japanese Gastric Cancer Association, “Japanese gastric cancer treatment guidelines 2010 (ver. 3),” *Gastric Cancer*, vol. 14, no. 2, pp. 113–123, Jun. 2011.
[8] F. Lordick *et al.*, “Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial.,” *Lancet. Oncol.*, vol. 14, no. 6, pp. 490–9, May 2013.
[9] E. Van Cutsem *et al.*, “Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group.,” *J. Clin. Oncol.*, vol. 24, no. 31, pp. 4991–7, Nov. 2006.
[10] Y. Yamada *et al.*, “Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer.,” *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.*, vol. 26, no. 1, pp. 141–8, Jan. 2015.
[11] D. Cunningham *et al.*, “Capecitabine and oxaliplatin for advanced esophagogastric cancer.,” *N. Engl. J. Med.*, vol. 358, no. 1, pp. 36–46, Jan. 2008.
[12] M. Salati, K. Di Emidio, V. Tarantino, and S. Cascinu, “Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer?,” *ESMO Open*, vol. 2, no. 3, p. e000206, Jul. 2017.
[13] S. J. Sym *et al.*, “A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy,” *Cancer Chemother. Pharmacol.*, vol. 71, no. 2, pp. 481–488, Feb. 2013.
[14] S. Hironaka *et al.*, “Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial.,” *J. Clin. Oncol.*, vol. 31, no. 35, pp. 4438–44, Dec. 2013.
[15] F. Graziano *et al.*, “A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer,” *Ann. Oncol.*, vol. 11, no. 10, pp. 1263–1266, Oct. 2000.
[16] C. S. Fuchs *et al.*, “Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial,” *Lancet*, vol. 383, no. 9911, pp. 31–39, Jan. 2014.
[17] H. Wilke *et al.*, “Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial,” *Lancet Oncol.*, vol. 15, no. 11, pp. 1224–1235, Oct. 2014.
[18] P. C. Thuss-Patience *et al.*, “Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO),” *Eur. J. Cancer*, vol. 47, no. 15, pp. 2306–2314, Oct. 2011.
[19] H. E. R. Ford *et al.*, “Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial,” *Lancet Oncol.*, vol. 15, no. 1, pp. 78–86, Jan. 2014.
[20] J. H. Kang *et al.*, “Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone.,” *J. Clin. Oncol.*, vol. 30, no. 13, pp. 1513–8, May 2012.
[21] T. Janowitz *et al.*, “Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction and oesophageal adenocarcinoma: a meta-analysis of patient-level data,” *Br. J. Cancer*, vol. 114, no. 4, pp. 381–387, Feb. 2016.
[22] K. Higuchi *et al.*, “Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial),” *Eur. J. Cancer*, vol. 50, no. 8, pp. 1437–1445, May 2014.
[23] B. M. X. H. Y. L. Y. W. Z. L. Yong Zhang, “Doublet Versus Single Agent as Second-line Treatment for Advanced Gastric Cancer: A Meta-analysis of 10 Randomized Controlled Trials,” *Medicine (Baltimore).*, vol. 95, no. 8, p. e2792, Feb. 2016.
[24] S.-E. Al-Batran *et al.*, “Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or

gastroesophageal junction adenocarcinoma," *Ann. Oncol.*, vol. 27, no. 4, pp. 673–679, Apr. 2016.
[25] K. Shitara *et al.*, "Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial," *Lancet Oncol.*, vol. 19, no. 11, pp. 1437–1448, Nov. 2018.
[26] C. S. Fuchs *et al.*, "Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer," *JAMA Oncol.*, vol. 4, no. 5, p. e180013, May 2018.
[27] K. Shitara *et al.*, "Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial," *Lancet*, vol. 392, no. 10142, pp. 123–133, Jul. 2018.
[28] "Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study. | 2019 ASCO Annual Meeting Abstracts." [Online]. Available: http://abstracts.asco.org/239/AbstView_239_251955.html. [Accessed: 20-Jul-2019].
[29] S. A. Lacy, D. R. Miles, and L. T. Nguyen, "Clinical Pharmacokinetics and Pharmacodynamics of Cabozantinib," *Clin. Pharmacokinet.*, vol. 56, no. 5, pp. 477–491, May 2017.
[30] R. Nadal *et al.*, "846OFinal results of a phase I study of cabozantinib (cabo) plus nivolumab (nivo) and cabonivo plus ipilimumab (Ipi) in patients (pts) with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies," *Ann. Oncol.*, vol. 28, no. suppl_5, Sep. 2017.
[31] N. Agarwal *et al.*, "872PPhase Ib study (COSMIC-021) of cabozantinib in combination with atezolizumab: Results of the dose escalation stage in patients (pts) with treatment-naïve advanced renal cell carcinoma (RCC)," *Ann. Oncol.*, vol. 29, no. suppl_8, Oct. 2018.
[32] B. A. McGregor *et al.*, "879PActivity of cabozantinib (cabo) after PD-1/PD-L1 immune checkpoint blockade (ICB) in metastatic clear cell renal cell carcinoma (mccRCC)," *Ann. Oncol.*, vol. 29, no. suppl_8, Oct. 2018.
[33] G. K. Abou-Alfa *et al.*, "Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma," *N. Engl. J. Med.*, vol. 379, no. 1, pp. 54–63, Jul. 2018.
[34] M. E. Keeler *et al.*, "Pembrolizumab (pembro) and cabozantinib (cabo) in patients (pts) with metastatic renal cell carcinoma (mRCC): Phase I results.," *J. Clin. Oncol.*, vol. 37, no. 7_suppl, pp. 600–600, Mar. 2019.
[35] "Worldwide cancer data | World Cancer Research Fund." [Online]. Available: https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data. [Accessed: 11-May-2019].
[36] Y.-K. Kang *et al.*, "Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial.," *Lancet (London, England)*, vol. 390, no. 10111, pp. 2461–2471, Dec. 2017.
[37] M. J. Turnage RH, Richardson KA, Li BD, "Sabiston Textbook of Surgery.," in *18th ed. St. Louis, Mo: WB Saunders; chap 43.*, 2008.
[38] O. Hamid *et al.*, "Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma," *N. Engl. J. Med.*, vol. 369, no. 2, pp. 134–144, Jul. 2013.
[39] R. Simon, "Optimal two-stage designs for phase II clinical trials.," *Control. Clin. Trials*, vol. 10, no. 1, pp. 1–10, Mar. 1989.
[40] A. Ivanova, B. F. Qaqish, and M. J. Schell, "Continuous toxicity monitoring in phase II trials in oncology.," *Biometrics*, vol. 61, no. 2, pp. 540–5, Jun. 2005.
[41] J. Borucka, "METHODS FOR HANDLING TIED EVENTS IN THE COX PROPORTIONAL HAZARD MODEL," 2014.
[42] D. I. Warton and F. K. C. Hui, "The arcsine is asinine: the analysis of proportions in ecology.," *Ecology*, vol. 92, no. 1, pp. 3–10, Jan. 2011.

12.0 APPENDICES

APPENDIX A

Performance Status Criteria

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

5	Dead.	0	Dead.

APPENDIX B

Pill Diary

UCI 18-124

Cabozantinib Patient Pill Diary

Patient Name:_____ MRN:_____ Cycle:_____

Cabozantinib will be taken daily at home, except for clinic days when it will be taken at the clinic.

Take_____tablet(s) of 20mg Cabozantinib tablets once daily every 21 days.

Cabozantinib will be taken at least one hour before or at least two hours after eating.

If doses of cabozantinib are missed or held, **do not make up for missed doses.**

Take each dose as close to the same time every day as possible.

Please record the date and time you take Cabozantinib.

Please remember to bring your bottles and Patient Pill Diary at each clinic visit.

	Date	Time	Number of Pills Taken/ Comments
Day 1			____ tablet(s) taken
Day 2			____ tablet(s) taken
Day 3			____ tablet(s) taken
Day 4			____ tablet(s) taken
Day 5			____ tablet(s) taken
Day 6			____ tablet(s) taken
Day 7			____ tablet(s) taken
Day 8			____ tablet(s) taken
Day 9			____ tablet(s) taken
Day 10			____ tablet(s) taken
Day 11			____ tablet(s) taken
Day 12			____ tablet(s) taken
Day 13			____ tablet(s) taken
Day 14			____ tablet(s) taken
Day 15			____ tablet(s) taken
Day 16			____ tablet(s) taken
Day 17			____ tablet(s) taken
Day 18			____ tablet(s) taken
Day 19			____ tablet(s) taken
Day 20			____ tablet(s) taken
Day 21			____ tablet(s) taken

APPENDIX C
Patient Information Cabozantinib

PATIENT INFORMATION
CABOMETYX™ (Ka-boe-met-iks)
cabozantinib
tablets

What is CABOMETYX?

CABOMETYX is a prescription medicine used to treat people with advanced kidney cancer (renal cell carcinoma) whose cancer has spread or grown after treatment with other cancer medications.

It is not known if CABOMETYX is safe and effective in children.

Before you take CABOMETYX, tell your healthcare provider about all of your medical conditions, including if you:

- have any unusual bleeding
- have high blood pressure
- plan to have any surgery, including dental surgery. You should stop treatment with CABOMETYX at least 28 days before any scheduled surgery.
- have liver problems
- are pregnant, or plan to become pregnant. CABOMETYX can harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment and for 4 months after your final dose of CABOMETYX. Talk to your healthcare provider about birth control methods that may be right for you. If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if CABOMETYX passes into your breast milk. Do not breastfeed during treatment and for 4 months after your final dose of CABOMETYX.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements. CABOMETYX and certain other medicines may affect each other causing side effects.

How should I take CABOMETYX?

- Take CABOMETYX exactly as your healthcare provider tells you to take it.
- **Do not** take CABOMETYX with food. **Do not** eat for at least 2 hours before and at least 1 hour after taking CABOMETYX.
- Swallow CABOMETYX tablets whole with a full glass (at least 8 ounces) of water.
- **Do not** crush CABOMETYX tablets.
- If you miss a dose and your next dose is in:
  - less than 12 hours, take your next dose at the normal time. Do not make up the missed dose.
  - 12 hours or more, take the missed dose as soon as you remember. Take your next dose at the normal time.

What should I avoid while taking CABOMETYX?

Do not drink grapefruit juice, eat grapefruit or supplements that contain grapefruit during treatment with CABOMETYX.

What are the possible side effects of CABOMETYX?
CABOMETYX may cause serious side effects, including:

- **severe bleeding (hemorrhage).** Tell your healthcare provider right away if you get any signs of bleeding during treatment with CABOMETYX, including:
  - coughing up blood or blood clots
  - vomiting blood or if your vomit looks like coffee-grounds
  - red or black (looks like tar) stools
  - menstrual bleeding that is heavier than normal
  - any unusual or heavy bleeding
- **a tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula).** Tell your healthcare provider right away if you get tenderness or pain in your stomach-area (abdomen).
- **blood clots, stroke, heart attack, and chest pain.** Get emergency help right away if you get:
  - swelling or pain in your arms or legs
  - shortness of breath
  - feel lightheaded or faint
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes

- sweating more than usual
- numbness or weakness of your face, arm or leg, especially on one side of your body
- sudden trouble walking
- dizziness, loss of balance or coordination
- a sudden severe headache

- **high blood pressure (hypertension).** Hypertension is common with CABOMETYX and sometimes can be severe. Your healthcare provider will check your blood pressure before starting CABOMETYX and during treatment with CABOMETYX. If needed, your healthcare provider may prescribe medicine to treat your high blood pressure.
- **diarrhea.** Diarrhea is common with CABOMETYX and can be severe. If needed, your healthcare provider may prescribe medicine to treat your diarrhea. Tell your healthcare provider right away, if you have frequent loose, watery bowel movements.
- **a skin problem called hand-foot skin reaction.** Hand-foot skin reactions are common and can be severe. Tell your healthcare provider right away if you have rashes, redness, pain, swelling, or blisters on the palms of your hands or soles of your feet.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen during treatment with CABOMETYX. Tell your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with CABOMETYX if you have certain side effects.

The most common side effects of CABOMETYX are:

- tiredness
- nausea
- decreased appetite
- vomiting
- weight loss
- constipation

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of CABOMETYX. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CABOMETYX?

- Store CABOMETYX at room temperature 68°F to 77°F (20°C to 25°C).

Keep CABOMETYX and all medicines out of the reach of children.

General information about CABOMETYX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CABOMETYX for a condition for which it was not prescribed. Do not give CABOMETYX to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about CABOMETYX that is written for health professionals.

What are the ingredients in CABOMETYX?

Active ingredient: cabozantinib

Inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

Manufactured for Exelixis, Inc. South San Francisco, CA 94080

For more information, go to www.cabometyx.com or call 1-855-292-3935.