Cabozantinib plus Pembrolizumab as First-Line Therapy for Cisplatin-Ineligible Advanced Urothelial Carcinoma (PemCab)

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS 3
LIST OF ABBREVIATIONS 5
PROTOCOL SIGNATURE 9
STUDY SUMMARY 10
1 OBJECTIVES 12
1.1 Primary Objective and Endpoint 12
1.2 Secondary Objectives and Endpoints 12
1.3 Exploratory Objectives and Endpoints 12
2 BACKGROUND 12
3 DRUG INFORMATION 15
3.1 Cabozantinib 15
3.2 Pembrolizumab 21
4 STUDY DESIGN 23
4.1 Description 23
4.2 Number of Patients 23
4.3 Number of Study Centers 23
4.4 Study Duration 23
4.5 Conditions for Terminating the Study 23
5 ELIGIBILITY CRITERIA 24
5.1 Pre-Screening Eligibility for Patients Scheduled for Urothelial Diagnostic Procedure (biopsy or surgery) 24
5.2 Inclusion Criteria 25
5.3 Exclusion Criteria 27
6 TREATMENT PLAN 32
6.1 Administration Schedule 32
6.2 Cabozantinib 32
6.3 Pembrolizumab (MK-3475) Treatment 34
6.4 Dose Calculation 36
6.5 Preparation of Infusion Solution 36
6.6 Administration 37
6.7 Accountability and Compliance 38
6.8 Concomitant Medications and Therapies 39
6.9 Duration of Therapy 44
7 TOXICITIES AND DOSEAGE MODIFICATION 45
7.1 Dose Modifications and Guidelines for Adverse Event Management for Cabozantinib 45
7.2 Dose modification and toxicity management guidelines for pembrolizumab 56
7.3 Contraception 60
7.4 Supportive Care 61
8 STUDY CALENDAR 62
9 STUDY PROCEDURES 64
9.1 Pre-Screening 64
9.2 Screening 64
9.3 On-Treatment Evaluations 64

9.4 End of Treatment Assessments (completed 28 days ± 14 days after completion of treatment 65
9.5 Follow-up Assessments 66
10 CRITERIA FOR EVALUATION AND ENDPOINT 66
10.1 Efficacy 66
10.2 Safety 67
11 STATISTICAL CONSIDERATIONS 68
11.1 Primary objective 68
11.2 Secondary Objectives and Endpoints 68
11.3 Exploratory Objectives and Endpoints 68
12 REGISTRATION GUIDELINES 69
13 DATA SUBMISSION SCHEDULE 69
14 SPECIAL INSTRUCTIONS 69
14.1 Correlative Studies 69
15 ETHICAL AND REGULATORY CONSIDERATIONS 71
15.1 Informed consent 71
15.2 Institutional Review 71
15.3 Data and Safety Monitoring Plan 71
15.4 Adverse Events / Serious Adverse Events 72
15.5 SAE Reporting Requirements 74
15.6 Reporting of Pregnancy 75
15.7 Medication Errors/Overdose 75
15.8 Protocol Amendments 75
15.9 Protocol Deviations 76
15.10 FDA Annual Reporting 76
15.11 Clinical Trials Data Bank 76
15.12 Record Keeping 76
16 PUBLICATIONS OF DATA 76
17 BIBLIOGRAPHY 77
APPENDIX A - Cabozantinib Dosing Diary 81
APPENDIX B- Stool Sample Collection Questionnaire 82

LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography

Abbreviation or Term[1]	Definition/Explanation
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio

Abbreviation or Term[1]	Definition/Explanation
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine

Abbreviation or Term[1]	Definition/Explanation
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator **Date**

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Principal Investigator Name (Print)

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Name of Institution

STUDY SUMMARY

Title	Cabozantinib plus pembrolizumab as first-line therapy for cisplatin-ineligible advanced urothelial carcinoma
Short Title	CaboPembro UC
Protocol Number	IRB#104688
IND	IND#139643
Phase	Phase II
Design	Single-arm, nonrandomized phase II study to test efficacy of combination pembrolizumab and cabozantinib.
Study Duration	Accrual will take approximately 1-2 years with 1 year of treatment and 6 months follow up. Total study duration 3-4 years.
Study Centers	This study will be conducted at the Huntsman Cancer Institute and up to two additional cancer centers.
Objectives	Primary Objective: Evaluate measurable disease overall response rate (ORR). Secondary Objectives: Evaluation of progression-free survival (PFS) at 6 months (PFS6), overall survival (OS), and evaluation of toxicities of the combination.
Number of Subjects	39 subjects will be enrolled to ensure 35 evaluable patients
Diagnosis and Main Eligibility Criteria	Cisplatin-ineligible urothelial carcinoma **Key Inclusion Criteria:** • Histologically proven transitional cell or urothelial carcinoma (UC). • Metastatic (any N+ or M1) or locally advanced, unresectable (T4bN0) disease. • Measurable disease is required as determined by RECIST v1.1. • Cisplatin-ineligibility based on ≥1 of the following: o Estimated CrCl of between ≥40 and <60 ml/min (CG formula) o ECOG PS≥2 o Hearing loss o Baseline neuropathy o Patient refusal **Key Exclusion Criteria:** • Prior chemotherapy for metastatic/ advanced urothelial carcinoma. • Prior chemotherapy treatment for localized urothelial carcinoma that has been completed less than 6 months before registration.

	• Small-cell or sarcomatoid component in histology.
Study Product, Dose, Route, Regimen	Pembrolizumab 200mg IV q 3 weeks with cabozantinib administered 40mg orally, with dose reductions to 20 mg daily. Subsequent dose reduction to 20 mg every other day to improve tolerability is allowed.
Duration of administration	Patients will receive therapy until treatment discontinuation criteria is met or until 12 months from start of therapy
Reference therapy	Study treatment will be compared to pembrolizumab as single agent.
Statistical Methodology	A 95% one-sided exact binomial confidence interval (Clopper-Pearson) will be calculated for ORR. With 35 evaluable subjects the lower bound of the 95% confidence interval will extend no more than 26% from the observed proportion. If there are 17 or more objective responses in 35 patients the confidence interval will exclude 32%. Secondary analyses will include an association of risk group (based on performance status and visceral metastasis) with PFS. Stratified Kaplan-Meier methodology will be used to associate risk group (based on performance status and visceral metastasis) with PFS.

1 OBJECTIVES

1.1 Primary Objective and Endpoint

To evaluate measurable disease overall response rate (ORR).

Endpoint: Subjects will be evaluated by CT scans at regular intervals for disease assessment by RECISTv1.1 criteria for the duration of treatment.

1.2 Secondary Objectives and Endpoints

1.2.1 To evaluate progression-free survival (PFS) at 6 months (PFS6).

Endpoint: Subjects will be evaluated by CT scans at regular intervals for disease assessment by RECISTv1.1 criteria for the duration of treatment.

1.2.2 To evaluate Overall Survival (OS).

Endpoint: Subjects will be evaluated using Kaplan-Meier estimation for survival for up to 6 months after discontinuation of study treatment; patients surviving longer than 6 months will be censored.

1.2.3 To evaluate toxicities associate with the combination treatment.

Endpoint: Adverse events will be collected beginning with study treatment and tabulated according to drug attribution.

1.3 Exploratory Objectives and Endpoints

1.3.1 To evaluate molecular markers for pharmacodynamic pathways associated with response.

Endpoints: Blood, tissue, and stool samples will be collected at various time points to measure molecular markers to correlate with response to develop a panel predictive of response which will be validated in future studies. Once the model is determined, statistical methods will be determined.

1.3.2 To evaluate ORR and PFS6 using immune specific disease assessment criteria

Endpoint: Subjects will be evaluated by CT scans at regular intervals for disease assessment by iRECIST criteria for the duration of treatment.

2 BACKGROUND

Currently the standard of care first-line therapy for urothelial carcinoma (UC) is cisplatin based chemotherapy. However, many patients diagnosed with UC are not eligible for cisplatin due to age, frailty or other comorbid conditions. In a retrospective analysis of 299 patients presenting in a community-based cancer center system with stage 4 disease, the regimens administered were cisplatin based in 107 patients (35.9%), carboplatin based in 81 (27.2%), and non-platinum based in 25 (8.4%).[1] Notably, no chemotherapy was administered in 71 (23.8%) patients. Cisplatin administration was more common in patients aged ≤70 years (62/150 [41.3%]) as opposed to >70 years (45/148 [30.4%]) (P = 0.05).

In another retrospective study of 1031 patients aged ≥66 years presenting with advanced bladder cancer in the SEER-Medicare linked database, among patients receiving chemotherapy, carboplatin accounted for 50.6%, cisplatin for 39.7% and other agents for 9.8%.[2] A relatively large proportion of patients did not receive chemotherapy in this Medicare database (48.4%), again highlighting the difficulties of administering aggressive chemotherapy in this population. The reasons for non-administration of cisplatin were not available in both of these studies, although it may be postulated that the presence of renal dysfunction, poor performance status, elderly age and comorbidities likely are responsible as these are frequent exclusion criteria for previously reported large phase III clinical trials of cisplatin based chemotherapy for UC.

Carboplatin is often substituted for cisplatin in cisplatin-ineligible patients, but is associated with inferior response rates, especially CR rates, which suggests the lack of potential cures. In a meta-analysis of randomized phase II trials, cisplatin-based chemotherapy was associated with a significantly higher likelihood of achieving a CR (relative risk {RR} = 3.54; 95% confidence interval {CI} 1.48-8.49; P = 0.005) and ORR (RR = 1.34; 95% CI 1.04-1.71; P = 0.02) compared to carboplatin-based chemotherapy.[3] Clearly, other tolerable and high-effective therapies are needed for this population of patients with cisplatin-ineligible invasive urothelial carcinoma.

In a previously reported study,[4] prognostic markers for poor clinical outcomes associated with disease progression were studied. The authors demonstrated that expression of Met was positively associated with histologic grade, stage classification, tumor size, and nodular tumor growth (P <.05, respectively) in urothelial carcinoma. Factors that predicted disease progression were tumor stage, Met status, and TP53 accumulation (P <.05, respectively). Indicators for poor long-term survival were invasive cancer, multiple tumors, and Met overexpression (P =0.0006, 0.01 and 0.04, respectively). The authors concluded that the c-met proto-oncogene plays a more important role in the progression of bladder carcinogenesis. Evaluation of Met expression could identify a subset of bladder cancer patients who may benefit from molecularly targeted therapy.

In a recent report, a positive association of Axl or platelet-derived growth factor receptor-alpha (PDGFR-α) with c-Met expression was demonstrated through preclinical models of disease.[5] The transactivation of c-Met on Axl or PDGFR-α in vitro was through a ras- and Src-independent activation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) pathway. In human bladder cancer, co-expression of these RTKs was associated with poor patient survival ($p < 0.05$), and overexpression of c-Met/Axl/PDGFR-α or c-Met alone showed the most significant correlation with poor survival ($p < 0.01$). Thus, in addition to c-Met, the cross-talk with Axl and/or PDGFR-α also contributes to the progression of human bladder cancer.

Finally, recent data[6] suggest significant activity for Met inhibition in bladder cancer. PF-2341066 (crizotinib), a small, orally available, highly specific Met-inhibitor was evaluated in an orthotopic xenograft model of bladder transitional cell carcinoma (TCC). Animals were treated with intra peritoneal PF-2341066 after positive detection of bladder tumor primary and/or metastatic disease. Fluorescence imaging (Xenogen IVIS) of mice was performed weekly. Mice were euthanized 4 weeks after the start of treatment and their tissues studied histologically. PF-2341066 was found to reduce tumor burden to below detectable levels in both primary and metastatic sites in all mice treated. No noticeable side effects were detected in treated mice secondary to drug administration. Thus, this was the first study to test a small orally available

Met-selective inhibitor in an orthotopic, HGF-driven model of human bladder cancer, supporting its potential use in patients with bladder cancer.

In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. This suggests that cabozantinib may be effective in urothelial carcinoma. This concept is currently being studied in an ongoing clinical trial evaluating the efficacy of single agent cabozantinib (NCT01688999), with final results expected soon. Preliminary results suggest clinical activity with single agent cabozantinib with objective radiographic responses seen.

Previously, immune-based treatments have demonstrated significant clinical benefit as single agent therapies in UC. To date, many different immunotherapies are approved with PD-1 antagonists (pembrolizumab, nivolumab) and PD-L1 antagonists (atezolizumab, avelumab, durvalumab). In the second-line pembrolizumab trial for patients with UC (KEYNOTE-045)[7], 542 patients were randomized to pembrolizumab or the treating physician's choice of chemotherapy (vinflunine, docetaxel or paclitaxel) with significant clinical benefit demonstrated in the pembrolizumab arm. The overall survival was improved at 10.3 months versus 7.4 months for pembrolizumab versus chemotherapy respectively (HR for death 0.73; 95% CI 0.59—0.91; P = 0.002). It was also better tolerated with decreased grade 3-5 adverse events (15.0% versus 49.4% respectively). Pembrolizumab is now one standard-of-care option that is FDA approved for UC in the second-line setting. Similarly, durvalumab[8], atezolizumab,[9] and nivolumab[10] have also demonstrated efficacy in the second-line setting, while pembrolizumab[11] and atezolizumab[12] have demonstrated efficacy in the first-line setting. Immunotherapy for urothelial carcinoma is clearly effective, active therapy in urothelial carcinoma. However, the primary challenge with these therapies is the relatively low response rate. In the KEYNOTE-045 clinical trial of second-line pembrolizumab for instance, there was a low 21.1% response rate for pembrolizumab compared to 11.4% with chemotherapy. Robust responses are frequently observed with immunotherapy, but unfortunately only a relatively few number of patients experience a response to this type of treatment.

Using both cabozantinib plus pembrolizumab in cisplatin-ineligible UC is attractive as this may be a well-tolerated and synergistically active combination. VEGFR therapy appears to modulate the immune system, suggesting possible clinical benefit for this combination. In mouse models, axitinib (another multi-targeted kinase inhibitor similar to cabozantinib) demonstrated a significant increase in the number of tumor infiltrating lymphocytes and altered the microenvironment from a suppressive to a stimulatory environment relative to vehicle controls.[13] Another study analyzing archival tissue from patients with metastatic renal cell carcinoma demonstrated a positive relationship between tumor-infiltrating lymphocytes and VEGF gene expression (r = -0.18; P = 0.089), suggesting that the VEGF pathway partially regulates the immune effect in kidney cancer. This theory has been tested in a pilot clinical trial of ten patients.[14] Patients were treated with 1 cycle of bevacizumab (a VEGF antagonist) prior to treatment with the combination of atezolizumab (a PD-L1 antagonist) and bevacizumab. Patients underwent biopsies at baseline, after the lead-in phase with bevacizumab and after two cycles of the combination therapy. The tumor tissue demonstrated an increase in gene signatures associated with Th1, CD8, and natural killer cell activity after treatment at all times in the study including after the bevacizumab-only period. This strongly suggests that the combination of VEGFR TKI and immunotherapy with PD-L1 therapy will be effective and safe in patients with

metastatic urothelial carcinoma. Perhaps most importantly, the combination of axitinib plus avelumab was recently reported in a phase IB clinical trial of 55 patients with metastatic renal cancer.[15] This combination appears to be relatively well tolerated with an incidence of grade 3-5 toxicities in 52% (axitinib related) and 20.0% (avelumab related) of patients. The confirmed overall response rate was 54.5% (95% CI 40.6—68.0) with 2 complete responses and 28 partial responses. Though this trial is in a different disease state than the proposed clinical trial, this combination of a VEGF targeted therapy plus a PD-1 antagonist appears to be safe and well tolerated, and potentially more active than single agent immunotherapy.

We hypothesize that the combination of cabozantinib plus pembrolizumab will be safe in cisplatin-ineligible patients as a first-line treatment. Also we hypothesize that this combination will demonstrate significant additive or synergistic activity resulting in a 20% increase in response in this disease compared to historic benchmarks for progression-free survival.

3 DRUG INFORMATION

3.1 Cabozantinib

3.1.1 Description

Cabozantinib is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6, 7-dimethoxyquinolin-4-yloxy) phenyl)-*N'*-(4-fluorophenyl) cyclopropane-1, 1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. Cabozantinib (*S*)-malate salt is a white to off-white solid that is practically insoluble in aqueous media.

Cabozantinib tablets are supplied as film-coated tablets containing 20 mg of cabozantinib, which is equivalent to 25 mg of cabozantinib (*S*)-malate. Cabozantinib also contains the following 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.

3.1.2 Pharmacology

Mechanism of Action

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.

Cardiac Electrophysiology

The effect of orally administered cabozantinib 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC. 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 cabozantinib-treated patients had a QTcF > 500 ms. Details can be found in the Investigator's Brochure

The effect of orally administered cabozantinib 140 mg qd on corrected QT interval (QTc) was evaluated in a placebo-controlled study in subjects with medullary thyroid cancer (evaluable subjects: cabozantinib arm, 209; placebo arm, 107). A mean increase in Fridericia's correction of QT interval (QTcF) of 10 - 15 ms was observed 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 patients 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.

Clinical Pharmacokinetics

Pharmacokinetics

A population PK analysis was conducted in subjects with RCC who received repeated oral daily cabozantinib tablet dosing at 60 mg (with protocol-permitted dose reductions to 40 mg and 20 mg) combined with healthy subjects who received a single oral cabozantinib tablet dose of 20, 40, or 60 mg. This analysis indicated that for a white male subject, the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (Vz) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h. Female gender and Asian race were significant covariates on CL/F, and while the attributes were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects.

Absorption and Distribution

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. 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. Cabozantinib is highly protein bound in human plasma (99.7%). A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose.

Metabolism and Elimination

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide 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. Within a 48-day collection period after a single dose of ^{14}C- cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Specific Populations

Renal Impairment

Cabozantinib should be used with caution in subjects with mild or moderate renal impairment. No formal pharmacokinetic study of cabozantinib has been conducted in patients with renal impairment. The results of a population pharmacokinetic analysis suggested that mild to moderate renal impairment (creatinine clearance value <30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib.

Hepatic Impairment

Cabozantinib should be used with caution and dose reductions may be warranted in subjects with mild or moderate hepatic impairment, and clinical monitoring is recommended for these subjects. Cabozantinib is not recommended for use in subjects with severe hepatic impairment as safety and efficacy have not been established in this population

The pharmacokinetics of cabozantinib has not been studied in patients with hepatic impairment.

Pediatric population: This study will not enroll pediatric patients.

Effects of Age, Gender and Race: A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11%). Cabozantinib pharmacokinetics was not affected by age (20-86 years).

Drug Interactions

CYP Enzyme Inhibition and Induction: cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsomal (HLM) preparations. IC50 values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control _ naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations (100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in patients with solid tumors.

P-glycoprotein inhibition: cabozantinib is an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Details can be found in the Investigator's Brochure.

3.1.3 Cabozantinib Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of cabozantinib have not been conducted. 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 cabozantinib. 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 equal to the human exposure by 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 (approximately 50% of the human exposure by 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 exposures equal to 6% and 3%, respectively, the human exposure by AUC at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately equal to the human exposure by AUC at the recommended dose) exhibited ovarian necrosis. Details can be found in the Investigator's Brochure.

3.1.4 Clinical Experience

Adverse Events

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, palmar plantar erythrodysesthesia syndrome (PPES), vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the most recent cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g., transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism), 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, leukopenia, and hyperglycemia.

Adverse events may occur 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. Please refer to section 7 for more specific details regarding Adverse Event descriptions and management.

Clinical Activity

Cabozantinib has demonstrated broad range of clinical anti-tumor activity in early Phase 1 and Phase 2 studies in Medullary Thyroid Carcinoma (MTC) and several other tumor types. In a randomized discontinuation trial (RDT) XL184-203, the following disease control rates (DCR = complete response [CR] + partial response [PR] + stable disease [SD]) at Week 12 were observed: non-small cell lung cancer (NSCLC), 38%; breast cancer, 48%; melanoma, 46%; ovarian cancer, 53%; HCC, 66%; and CRPC, 66%. Observations of clinical activity have included decrease of soft tissue tumor lesions including visceral metastases, effects on metastatic lesions on bone scan (partial or complete bone scan resolution), reduction in serum markers of bone resorption and formation, reduction in circulating tumor cells (CTCs; subjects with prostate cancer), increases in hemoglobin, and improvements in bone pain and reductions in narcotic use in subjects with bone metastases. In the placebo-controlled Phase 3 study XL184-301 in 330 MTC subjects, a significant increase in median PFS was seen in the cabozantinib arm compared with placebo (11.2 vs 4.0 months; hazard ratio [HR] =0.28; 95 CIs: 0.19, 0.40) with durable response (median of 14.6 months). An unplanned administrative analysis of overall survival (OS) performed at the request of the FDA with a data cut-off of 15 June 2012 (75% of required deaths) showed a trend for improved duration of OS in the cabozantinib arm compared with placebo (26.0 months vs 20.3 months; HR = 0.83; 95% CI: 0.60, 1.14).

In the Phase 2 study XL184-203, cabozantinib demonstrated broad clinical activity in men with CRPC. During the RDT phase, the majority of CRPC subjects with bone metastases and elevated total alkaline phosphatase (t-ALP) levels at baseline showed reductions in t-ALP [16]. These effects were independent of prior or concomitant bisphosphonate treatment. Subjects achieved a bone scan response (BSR) in both the 100 mg and 40 mg assigned NRE dose cohorts (73% and 45%, respectively). In addition, cabozantinib treatment has shown effects on bone metastases (by computed tomography [CT], or bone scan) in five tumor types, including CRPC, breast cancer, DTC (papillary), melanoma, and RCC. These effects include partial or complete bone scan resolution associated with reduction in circulating markers of bone resorption and formation, reduction in CTCs (CRPC), increases in hemoglobin, improvements in bone pain, and reductions in narcotic use.

The preliminary analysis of an ongoing phase II study with cabozantinib in patients with heavily pretreated relapsed or refractory advanced UC revealed promising clinical activity (NCT01688999) [17, 18]. Preliminarily, responses have been observed in 13% of 26 patients and associated with low peripheral blood regulatory T cells (Tregs). Moreover, cabozantinib decreased Tregs and increased PD-1 expression in Tregs, suggesting a potential role for combination or sequencing with immunotherapy.

CTEP Study: A Phase II Study of Cabozantinib (XL184) in Subjects with Advanced/Metastatic Urothelial Carcinoma

A total of 67 eligible subjects with diagnoses of progressive metastatic carcinoma of the bladder, urethra, ureter, or renal pelvis were enrolled in three cohorts: Cohort 1 (n=50), metastatic UC; Cohort 2 (n=6), bone only metastatic UC; Cohort 3 (n=11), non-UC (rare histologies).[26] Subjects were treated with 60 mg cabozantinib orally qd.

In Cohort 1, ORR for 42 evaluable subjects was determined to be 19.1% with 7 PRs and 1 CR. Median PFS for these subjects was 3.7 months (95% CI: 3.1, 6.5), and median OS was 8.0 months (95% CI: 5.2, 10.3) with 27.2% of subjects still alive 12 months after starting study treatment. Median OS among responders (n=8) was 21.5 months (95% CI: 7.3, 36.0). The median PFS for evaluable subjects with bone-only disease (Cohort 2, n=5) was 5.3 months (95% CI: 1.8, 8.3), and median OS was 9.3 months (95% CI: 3.6, 12.5). For evaluable subjects with non-urothelial rare histologies (Cohort 3, n=10), median PFS was 2.9 months (95% CI: 1.8, 3.7), and median OS was 4.6 months (95% CI: 2.6, 8.0).

Across all cohorts (n=67), the most frequently reported cabozantinib-related AEs were anemia (94%), PPES (83%), fatigue (69%), diarrhea (67%), AST increased (59%), platelet count decreased (58%), hypoalbuminemia (55%), hypophosphatemia (49%), creatinine increased (38%), nausea (36%), and hypothyroidism (40%); most of these AEs were Grade 1 or 2. The most frequent Grade 3 AEs related to cabozantinib were fatigue (9%), hypertension (7%), hypophosphatemia (6%), AST increased (4%), platelet count decreased (4%), diarrhea (3%), abdominal pain (3%), hyponatremia (3%), lymphocyte count decreased (3%), and proteinuria (3%). Grade 4 AEs were reported for hypomagnesemia (3%) and lipase increased (1%); no Grade 3 events were reported for either of these terms.

CTEP Study: A Phase I/Expansion Study of Cabozantinib plus Nivolumab Alone or With Ipilimumab in Subjects with Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

In an ongoing Phase 1 clinical trial in subjects with refractory metastatic UC and other genitourinary tumors, cabozantinib has been evaluated in combination with nivolumab, a monoclonal antibody to PD-1, and in combination with both nivolumab and ipilimumab, a monoclonal antibody to CTLA-4 (CaboNivo and CaboNivoIpi, respectively).[27] Forty-three (43) of 48 subjects enrolled were assessed for tumor response at the time of analysis (CaboNivo 26 subjects; CaboNivoIpi: 17 subjects). The ORR was 38% in the CaboNivo cohort (8 PRs and 2 CRs) and 18% in the CaboNivoIpi cohort (2 PRs and 1 CR); among the 16 evaluable metastatic UC subjects across both cohorts, the ORR was 38% (4 PRs and 2 CRs).

CaboNivo and CaboNivoIpi were well-tolerated among all enrolled subjects, and no DLTs were reported. Grade 3 AEs among subjects in the CaboNivo cohort irrespective of relationship to study treatment comprised neutropenia (n=5), hypophosphatemia (n=4), hypertension (n=3), dehydration, diarrhea, fatigue, lipase increased (each n=2), amylase increased, anemia, aseptic meningitis, hyperthyroidism, hyponatremia, proteinuria, thrombocytopenia, thromboembolic event, vomiting (each n=1); Grade 3 AEs among subjects in the CaboNivoIpi cohort comprised hypertension, hypophosphatemia (each n=3), fatigue, hyponatremia, lipase increased, nausea (each n=2), alanine aminotransferase

increased, anorexia, colitis, rash (each n=1). Grade 4 AEs in the CaboNivo cohort comprised lipase increased (n=2) and thrombocytopenia (n=1); there was one Grade 4 AE of lipase increased in the CaboNivoIpi cohort. There were no Grade 5 AEs.

More details regarding the efficacy of cabozantinib can be found in the Investigator's Brochure.

3.1.5 Translational Medicine

In preclinical studies, cabozantinib has shown potent anti-angiogenic, tumor growth inhibition, and tumor regression effects in vivo. In addition, cabozantinib blocked metastasis and improved overall survival in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer [19]. In human prostate and breast xenograft models, cabozantinib blocked osteoblastic and osteolytic progression of tumors in bone. Cabozantinib inhibited progression of multiple prostate cancer cell lines in bone metastatic and soft tissue murine models of prostate cancer and exerted a dose-dependent biphasic effect on osteoblast activity and inhibitory effect on osteoclast production in vitro [20] Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, the duration of action for cabozantinib was sustained, with > 50% inhibition observed for > 8 hours post-dose at a single dose level of 100 mg/kg [21] Anti-tumor effects of cabozantinib, were also examined in cultured HCC cells as well as in vivo models. In cultured HCC cells that are refractory to sorafenib and expressed p-MET (phosphorylated-MET), the cabozantinib inhibited the activity of MET and its downstream effectors, leading to G1 phase arrest with relatively more profound efficacy in p-MET-positive HCC xenografts [22]. Details can be found in the Investigator's Brochure.

3.2 Pembrolizumab

Refer to the most recent Investigator's Brochure (IB) for detailed background information on MK-3475 (Pembrolizumab).

3.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I

transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

3.2.2 **Preclinical and Clinical Trial Data**

Refer to the most recent Investigator's Brochure for Preclinical and Clinical data.

3.2.3 **Rationale for Dose Selection/Regimen/Modification**

PK data analysis of MK-3475 administered Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. This clinical trial uses the FDA approved dose and schedule for treatment of metastatic urothelial carcinoma.

4 STUDY DESIGN

4.1 Description

This is an open label, non-randomized phase 2 study of the combination of pembrolizumab and cabozantinib to assess overall response rate (ORR), progression free survival at 6 months (PFS6), and overall survival (OS) in patients with metastatic urothelial carcinoma (UC) ineligible for cisplatin. Cabozantinib is administered at 40 mg oral daily. Pembrolizumab will be administered at a fixed dose of 200mg intravenously every 3 weeks for all patients. A safety analysis will be performed after the first 6 patients enroll and receive treatment. During this stage, the decision to continue enrollment will be made by the Data Safety and Monitoring Committee (DSMC). When all 6 subjects in the have been followed for at least 21 days following first dose of pembrolizumab and cabozantinib, all available safety data will be considered in a decision to continue enrollment. Therapy continues until progression or intolerable toxicities. Study treatment may continue beyond initial radiographic or clinical disease progression as long as the patient is deriving clinical benefit from the treatment, as assessed by the investigator. Patients removed from therapy without evidence of progression will undergo radiological examination every 12 weeks or earlier if clinically warranted.

4.2 Number of Patients

A total of up to 39 subjects will be enrolled with the objective of having a minimum of 35 evaluable subjects for the primary objective.

4.3 Number of Study Centers

This is a multisite study to be conducted at Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah. Up to two additional sites may be included.

4.4 Study Duration

We anticipate up to 2 years to complete enrollment followed by 1 year of treatment and 5 months follow up. Total duration of the trial will be 3-to-4 years.

4.5 Conditions for Terminating the Study

At any time, the study may be terminated by the study sponsor or by Exelixis as described in the clinical trial agreement.

5 ELIGIBILITY CRITERIA

5.1 Pre-Screening Eligibility for Patients Scheduled for Urothelial Diagnostic Procedure (biopsy or surgery)

This eligibility checklist is used to determine a subject's eligibility for pre-screening correlative tissue collection. It must be filed in the subject's research chart with the enrolling investigator's signature.

Patient No. _____

Patient's Initials: (L, F, M) _____

5.1.1 **Inclusion Criteria**
Yes/No (Response of "no" = patient ineligible)

5.1.2 _____ Male or female subject aged ≥ 18 years.

5.1.3 _____ Clinically, subject is a candidate for urothelial diagnostic procedure (fresh soft-tissue biopsy or TURBT).

5.1.4 _____ Subject meets general medical criteria for consideration of treatment with immunotherapy using a checkpoint inhibitor.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto the pre-screening portion of this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

This eligibility checklist is used to determine patient eligibility and filed with enrolling physician's signature in the patient research chart.

Patient No. _____
Patient's Initials: (L, F, M) _____

5.2 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.2.1 _____ Histologically proven transitional cell or urothelial carcinoma.

5.2.2 _____ Patients with locally advanced or metastatic urothelial carcinoma *must meet one of the following*:

- Patients who are not eligible for cisplatin-containing chemotherapy AND whose tumors express PD-L1 (Combined Positive Score (CPS) ≥ 10 as determined by an FDA-approved test

  OR
- Patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

5.2.3 _____ Metastatic (any N+ or M1) or locally advanced, unresectable (T4bN0) disease.

5.2.4 _____ Measurable disease is required as determined by RECIST v1.1.

5.2.5 _____ Performance Status ECOG 0-2

5.2.6 _____ Cisplatin-ineligibility based on ≥1 of the following:

- Estimated creatinine clearance between ≥30 and <60 ml/min (Cockcroft-Gault formula)
- ECOG PS>1
- Hearing loss
- Baseline neuropathy > grade 1.
- Patient refusal

5.2.7 _____ Be ≥ 18 years of age on day of signing informed consent.

5.2.8 _____ Serum albumin ≥ 2.8 g/dl

5.2.9 _____ Alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN with documented bone metastases.

5.2.10 _____ Negative serum or urine pregnancy test at screening for women of childbearing potential (see section 7.3).

5.2.11 _____ Highly effective contraception for both male and female subjects throughout the study and for at least 120 days after last pembrolizumab treatment administration if the risk of conception exists (section 7.3).

5.2.12 _____ Must have recovered from adverse effects of any prior surgery, radiotherapy or other antineoplastic therapy to grade ≤2. If not recovered to grade ≤ 2, these must be deemed to be irreversible adverse events related to prior surgery and /or radiation therapy (such as incontinence or sexual dysfunction) per investigator clinical judgment.

5.2.13 _____ Recovery to baseline or ≤ Grade 2 CTCAE v.5.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. Alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

5.2.14 _____ Last dose of any radiation therapy > 2 weeks before first dose of study treatment.

5.2.15 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2.16 _____ Adequate organ function as defined as:

- ☐ **Hematologic:** Absolute neutrophil count (ANC) ≥ 1.5×10^9/L (without granulocyte colony-stimulation factor support within 2 weeks of screening), platelet count ≥ 100×10^9/L (without platelet transfusion within 2 weeks of screening), hemoglobin ≥ 9 g/dL (may have been transfused), and white blood cell count (WBC) ≥ 2.5×10^9/L.

- ☐ **Hepatic:** Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) (≤ 3 × ULN for subjects with Gilbert's disease / or unconjugated hyperbilirubenemia) and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 3 × ULN for subjects with documented metastatic disease. Patient with a history of unconjugated hyperbilirubinemia with otherwise acceptable liver enzyme levels (as per above criteria) may have higher bilirubin levels.

- ☐ **Renal:** Urine protein/creatinine ratio (UPCR) ≤ 2 mg/mg (≤ 113.2 mg/mmol) and serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault

equation:

- Males: (140 – age) × weight [kg]/(serum creatinine [mg/dL] × 72)
- Females: [(140 – age) × weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85

5.3 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.3.1 _____ Prior chemotherapy for metastatic urothelial carcinoma.

5.3.2 Prior chemotherapy for localized urothelial carcinoma that has been completed less than 6 months before registration.

5.3.3 _____ Variant histologies other than urothelial carcinoma will not be allowed. Patients with a component of variant histologies will be allowed to enroll, if urothelial carcinoma is the predominant histology per investigator judgement. Patients with any component of small cell will be excluded.

5.3.4 _____ Has received prior treatment with cabozantinib.

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

5.3.6 _____ Receipt of any type of cytotoxic, biologic, or other systemic anticancer therapy (including investigational) within 4 weeks before first dose of study treatment.

5.3.7 _____ Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or other checkpoint inhibitors previously.

5.3.8 _____ Radiation therapy for bone metastasis ≤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.

5.3.9 _____ Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

5.3.10 ____ Concomitant anticoagulation with oral coagulants except for those specified below.

Allowed anticoagulants are the following:

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

5.3.11 _____ The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × ULN within 14 days before the first dose of study treatment.

5.3.12 _____ The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
  - Ongoing congestive heart failure exacerbation or New York Heart Association Class 4, unstable angina pectoris, serious cardiac arrhythmias.
  - Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment. Uncontrolled hypertension needs to be determined based on persistently high blood pressure readings over more than 24 hours and should NOT be based on the blood pressure readings from one clinic visit. Blood pressure readings done at home or by primary care providers are acceptable. If a blood pressure reading on the day of screening is high, but there are documented acceptable (≤150 mm Hg systolic and ≤100 mm Hg diastolic) blood pressure readings prior to or after the screening visit (with or without the use of anti-hypertensive medications), patient will not be considered to have uncontrolled hypertension.
  - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or symptomatic thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) occuring less than or equal to 6 months before first dose of cabozantinib. [Note: Subjects with a diagnosis of deep vein thrombosis (DVT) or incidentally detected asymptomatic and sub-segmental pulmonary embolism (PE) on routine scans are allowed if on a stable dose of anti-coagulation for at least 1 week before first dose of study treatment]
  - Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose.

- Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
  - The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
  - Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.

  Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
- Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
- Lesions invading or encasing any major blood vessels.
- Other clinically significant disorders that would preclude safe study participation per investigator clinical judgement.
  - Serious non-healing wound/ulcer/bone fracture.
  - Uncompensated/symptomatic hypothyroidism.
  - Moderate to severe hepatic impairment (Child-Pugh B or C).

5.3.13 _____ Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

5.3.14 _____ Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications per investigator clinical judgement from prior surgery are not eligible.

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

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

5.3.16 _____ Diagnosis of another malignancy within 2 years before first dose of study treatment, with the exception of those determined by the treating investigator to have a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ treated surgically with curative intent, localized prostate cancer treated with curative intent and/or no intent for further treatment, or incidental prostate cancer).

5.3.17 _____ Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

5.3.18 _____ Has active autoimmune disease currently requiring systemic treatment with high dose corticosteroids (dose more than physiologic replacement doses equivalent to prednisone 10 mg daily) or disease modifying immunosuppressive agents). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, intranasal, inhaled, topical steroids, or local steroid injection) is not considered an exclusion.

5.3.19 _____ Active autoimmune disease that might deteriorate significantly when receiving an immuno-stimulatory agent per treating physician's clinical judgment. Subjects with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

5.3.20 _____ Prior organ transplantation including allogenic stem-cell transplantation.

5.3.21 _____ Has known history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

5.3.22 _____ Has an active infection currently requiring systemic (intravenous) antibiotic therapy.

5.3.23 _____ Has a known history of active TB (Bacillus Tuberculosis).

5.3.24 _____ Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

5.3.25 _____ Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

5.3.26 _____ Active and inactive vaccinations within 4 weeks of the first dose of pembrolizumab is prohibited.

5.3.27 _____ Known prior severe hypersensitivity to investigational products or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v.5.0 Grade ≥ 3).

5.3.28 _____ Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

5.3.29 _____ Subjects taking prohibited medications as described in Section 6.8. A washout period of prohibited medications for a period of at least two weeks or as clinically indicated should occur prior to the start of treatment.

5.3.30 _____ Inability to swallow tablets or evidence of impaired intestinal absorption

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

6 TREATMENT PLAN

Treatment should be administered on Day 1 of each cycle after all procedures and assessments have been completed as detailed on the Study Calendar (Section 8). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle.

All trial treatments will be administered on an outpatient basis.

6.1 Administration Schedule

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Cabozantinib is administered at 40 mg oral daily (with dose reductions to 20 mg daily; a subsequent dose reduction to 20 mg every other day to improve tolerability is allowed). Therapy continues until progression or intolerable toxicities. Study treatment may continue beyond initial radiographic or clinical disease progression as long as the patient is deriving clinical benefit from the treatment, as assessed by the investigator. A safety analysis will be performed after the first 6 patients enroll and receive treatment. During this stage, the decision to continue enrollment will be made by the Data Safety and monitoring committee (DSMC), when all 6 subjects have been followed for at least 21 days following first dose of pembrolizumab and cabozantinib. All available safety data will be considered in a decision to continue enrollment. Patients removed from therapy without evidence of progression will undergo radiological examination every 12 weeks or earlier if clinically warranted.).

6.2 Cabozantinib

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

Clinical Supplies will be provided by Exelixis.

6.2.1 Investigational Treatment

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

6.2.2 Cabozantinib Tablets

Exelixis internal number: XL184

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. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round in shape. The components of the tablets are listed in Table 6 1.

Table 6.1: Cabozantinib Tablet Components and Composition

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

6.2.3 **Dose, Schedule, and Route**

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily (with dose reductions to 20 mg daily, and subsequently 20 mg every other day to improve tolerability is allowed). The first dose will be given in clinic on day 1 of each cycle under supervision while the patient will take the rest of the medications at home. Patients will be provided with a dosing diary to keep track of medication taken (Appendix I).

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 7 below.

6.2.4 **Accountability and Compliance**

Accountability and compliance should be handled per institutional policies for commercially available medications. Patients will be provided with a dosing dairy to track oral dosing of cabozantinib (Appendix I).

All study drugs will be stored at the Huntsman Cancer Institute Investigational Pharmacy in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor, and will be inaccessible to unauthorized personnel. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent.

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form. Subject compliance with the treatment and protocol

includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

Instructions on medication resupply and destruction will be made available to affected parties as applicable.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Exelixis.

6.2.5 Post-Treatment Period

Subjects will return to the study site approximately 28 days after their last dose of cabozantinib to complete end-of-study assessments.

Laboratory and physical examinations will be performed. Remaining study treatment will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

6.3 Pembrolizumab (MK-3475) Treatment

6.3.1 How Supplied, Stored, Packaged, and Labeled

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided as Standard of Care by the Huntsman Cancer Institute pharmacy.

Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

6.3.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.3.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.3.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

6.3.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.3.6 Preparation and Administration

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C) and protected from light.

Note: vials should be stored in the original box to ensure the drug product is protected from light.

Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry.

Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion

In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED.

DO NOT SHAKE OR FREEZE THE VIAL(S).

DO NOT ADMINISTER THE PRODUCT AS AN (INTRAVENOUS (IV) PUSH OR BOLUS).

DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

Any departure from the guidance listed in this protocol, must be discussed with sponsor

6.4 Dose Calculation

200 mg Fixed Dose

- 2 vials (100 mg/4 mL)
- 8 mL total

6.5 Preparation of Infusion Solution

Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or hood since no anti-microbial preservative is present in the solutions.

Equilibrate required number of pembrolizumab MK-3475 vials to room temperature.

The preferred method of dose preparation is the volumetric method; gravimetric method is not permitted.

Choose a suitable infusion bag size so that the following conditions are met:

- Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
- The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.

Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline. The following infusion bag materials are compatible with pembrolizumab (MK-3475):

- PVC plasticized with DEHP
- Non-PVC (polyolefin)
- EVA
- PE lined polyolefin

Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag.

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL).

Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above.

If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL).

Note: If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.

Discard any unused portion left in the vial as the product contains no preservative.

6.6 Administration

Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

The following infusion set materials are compatible with (pembrolizumab) MK-3475:

- PVC Infusion set that is plasticized using DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set

- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing.

Document volume administered according to data entry guidelines.

In case of infusion reactions, infusion rate may differ; refer to protocol section 7.2 for specific instructions.

Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.

Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e., 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.

UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.

6.7 Accountability and Compliance

The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.8 Concomitant Medications and Therapies

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered up to 30 days after the last dose of trial treatment should be recorded in the appropriate CRF.

6.8.1 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the CRF.

6.8.2 Allowed Therapies

- Granulocyte colony stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines). Not allowed within two weeks prior to screening.
- Drugs used to control bone loss (e.g., bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require Principal Investigator approval.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice. Treatments are prohibited within two weeks prior to screening.
- 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 at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulatin regimen or the tumor.

After first dose of study treatment:

- Low dose low molecular weight heparins (LMWH) for prophylactic use after first dose of study treatment are allowed if clinically indicated (e.g., for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 7.
- Thereapeutic 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 outweights the risk per the investigator's discretion.

Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (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.

- Potential drug interactions with cabozantinib are summarized in Section 6.8.5.

6.8.3 **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 nonprotocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

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

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed on the RECIST v1.1 measurable lesions. Initiation of local anticancer therapy (e.g., palliative radiation) will be considered as progression of disease.
- 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.
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued study 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, and their products may also increase plasma concentrations of cabozantinib and should be avoided.
- Additional information on potential drug interactions with cabozantinib is provided in Section 6.8.5.

6.8.4 **Potential Drug Interactions with Cabozantinib**

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

unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

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

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

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways: http://medicine.iupui.edu/clinpharm/ddis/table.aspx OR http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

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

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

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

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

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

Table 6.2: Clinically Significant Interactions Involving Drugs that Affect Cabozantinib

Strong CYP3A4 Inhibitors	
Clinical Implications:	• Concomitant use of cabozantinib with a strong CYP3A4 inhibitor increased the exposure of cabozantinib compared to the use of cabozantinib alone • Increased cabozantinib exposure may increase the risk of exposure-related toxicity.
Prevention or Management:	Reduce the dosage of cabozantinib if concomitant use with strong CYP3A4 inhibitors cannot be avoided
Examples:	Boceprevir, clarithromycin, conivaptan, grapefruit juice[a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole
Strong CYP3A4 Inducers	
Clinical Implications:	• Concomitant use of cabozantinib with a strong CYP3A4 inducer decreased the exposure of cabozantinib compared to the use of cabozantinib alone • Decreased cabozantinib exposure may lead to reduced efficacy.
Prevention or Management:	Increase the dosage of cabozantinib if concomitant use with strong CYP3A4 inducers cannot be avoided
Examples:	Rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John's Wort[b]

a. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

b. The effect of St. John's Wort varies widely and is preparation-dependent and is prohibited.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.9 Duration of Therapy

Subjects enrolled after Amendment 7 (version date 08NOV2021) will remain on study treatment for up to 12 months. After consultation with PI, subjects enrolled prior to Amendment 7 (version date 08NOV2021) who have demonstrated a response to study treatment may continue beyond 12 months of treatment, if there is demonstrated continued clinical benefit.

Study treatment may continue beyond initial radiographic or clinical disease progression for up to 12 months as long as the patient is deriving clinical benefit from the treatment, as assessed by the investigator.

Subjects must be withdrawn from the study treatment for the following reasons:

- Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Radiographic disease progression by RECIST v1.1 (progression must be confirmed with follow up scan no less than 4 weeks and no more than 8 weeks after the first scan shows disease progression). Study treatment may continue beyond initial radiographic disease progression as long as the patient is deriving clinical benefit from the treatment, as assessed by the investigator.
- Progressive disease (PD), without clinical benefit, as determined by the investigator.
- Specific conditions described in the Management of Adverse Events Section 7.
- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment.
- Subject is lost to follow-up.
- Necessity for treatment with other treatment prohibited by protocol.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 120 days after discontinuation of study treatment.
- Women who become pregnant or are breastfeeding.
- If the 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 upon resolution of the toxicity.
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol.
- Significant noncompliance with the protocol schedule in the opinion of the investigator.

- The starting dose of Cabozantinib study treatment will be 40 mg once daily (qd), (with dose reduction allowed for documented adverse events to 20 mg daily, and then to 20 mg every other day to improve tolerability.)

Subjects may be withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

7.1 Dose Modifications and Guidelines for Adverse Event Management for Cabozantinib

Subjects will be monitored for AEs from the start of treatment through 30 days after the date of the last dose of cabozantinib treatment. Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.5.0. The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 40 mg/day. Dose reductions are permitted per PI discretion (see Table 7.1). Dose re--escalation level (See 7.2) of cabozantinib is permitted.
- Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.
- Interruption of cabozantinib treatment for AEs may occur at any time per investigator discretion. If treatment is interrupted due to AEs for more than 6 weeks, all study treatment should be 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 upon resolution of the toxicity.

- Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Table 7.1

Assigned dose	Dose Level Reduction
40-mg cabozantinib oral, qd	20-mg cabozantinib oral, qd.
20-mg cabozantinib oral, qd	20-mg cabozantinib oral, qad

Table 7.2

Assigned dose	Dose Level Escalation
20-mg cabozantinib, oral qad	20-mg cabozantinib, oral qd
20-mg cabozantinib, oral qd	40-mg cabozantinib, oral qd

Table 7.3: Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.5.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs that are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs that are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Permanently discontinue all study treatment unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 7.1.1. For re-treatment criteria of study treatment after a dose hold see Section 7.1.1.
[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

7.1.1 Guidelines for Management of Potential Adverse Events for Cabozantinib

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

All study treatment should be permanently 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).

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 are present.

Permanently discontinue all study treatment 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 7.4. 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 7.4: 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 (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (e.g., small lactose-free meals, bananas, and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and permanently discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o 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 (e.g., stool sample for culture) o Administer antibiotics as needed (e.g., 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 o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose o Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., 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 6.8.5).

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.

Permanently discontinue all study treatment 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.

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

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 the 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 rivoroxaban, edoxaban, or apixaban are allowed for the management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardio protection per local applicable guidelines are not allowed, until 4 weeks ater cabozantinib has been permanently discontinued.

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.

Hypertension: Table 7.5 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.

All study treatment should be permanently discontinued in subjects with hypertensive emergency.

Table 7.5: 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 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]	• Decide to initiate or adjust antihypertensive. Permanently discontinue all study treatment

[a] The investigator may approve 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 and PI discretion.
[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, 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 (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

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

Skin and Subcutaneous Tissue Disorders: Wound healing and surgery: 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 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including 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 7.6.

Table 7.6: 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 (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., 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 (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Permanently 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: 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.

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 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Proteinuria: Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 7.7 provides treatment guidelines for proteinuria deemed related to cabozantinib.

All study treatment should be permanently 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 7.7: 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	• Permanently discontinue all study 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. All study treatment should be permanently discontinued in subjects with RPLS.

Hepatocellular Toxicity: Investigators should monitor for DILI diligently and report any potential events.

Elevation of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevations of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible,

hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other potential causes for these increases (e.g., cancer-related infection) should be evaluated. Management guidance for hepatoxocity related to cabozantinib is provided in Table 7.8.

Table 7.8: Management of Liver Function Laboratory Abnormalities Related to Cabozantinib

Severity of ALT, AST, Total Bilirubin Elevations by CTCAE v.5.0	**Treatment Dose Modification**
Grade 1	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2	• Interrupt study treatment if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart study treatment after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade ≥ 3	• Interrupt study treatment and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart study treatment at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment. • Discontinue if drug-related ALT or AST>3 X ULN in combination with total bilirubin >2 X ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE v.5.0, Common Terminology Criteria for Adverse Events version 4

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.

The following condition requires discontinuation of cabozantinib:

Drug-related ALT or AST >3 × ULN in combination with total bilirubin >2 × ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).

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 adequate healing has taken place.

Blood and Lymphatic System Disorders: Hematological toxicities (i.e., 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 (e.g., 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, permanently 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.
- 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.
- Administration and is treatable/has been resolved.

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

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

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. 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 (e.g., 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.

7.2 Dose modification and toxicity management guidelines for pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7.9.

Table 7.9: Dose modification and toxicity management guidelines for immune-related AEs associated with Pembrolizumab.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.

   For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAE v.5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		

Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Serum Creatinine Increased	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
NOTES: 1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. 2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)				

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.10.

Table 7.10: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None

Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v.5.0 (CTCAE) at http://ctep.cancer.gov

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the study sponsor (principal investigator). The reason for interruption should be documented in the patient's study record. Patients with a planned interruption may continue on the study with monotherapy of the other agent. Patients may also continue on the study with a planned permanent discontinuation of one of the study medications.

7.3 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)

- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

8 STUDY CALENDAR

1 cycle = 3 weeks ± 3 days

Examination	Pre-screening[23]	Screening[1]	C1, 5, 9… Day 1[2]	C2, 6, 10… Day 1	C3, 7, 11… Day 1	C4, 8, 12… Day1	End of Treatment[20]	Follow-up[21]
Informed consent	X	X						
Medical history		X						
Eligibility criteria	X	X						
Vital signs, weight		X	X	X	X	X	X	
Height		X						
Physical examination[3]		X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	
Viral Hepatitis Screening[4]		X						
Smoking History		X						
Hematology[5]		X	X	X	X	X	X	
Chemistry[6]		X	X	X	X	X	X	
LDH, Lipase, Lipid Panel, GGT[7]		X				X	X	
BNP[22]		X				X	X	
Urinalysis[8]		X	X	X	X	X	X	
Coagulation[9]		X				X	X	
Thyroid Function Test[10]		X				X	X	
Pregnancy test[11]		X		X		X		
ECG[12]		X				X		
Concomitant Medications		X						
Adverse Event Assessment			X					
CT Scans (c, a, p)[13]		X				X[13]	X	X[21]
Bone Scans[14]		X	X				X	X
Optional Tissue for Correlative Studies[15]	X	(X)[15]				X		
Optional Blood for Correlative Studies[16]			X	X	X	X	X	
Optional Stool for Correlative Studies[17]			X	X	X	X	X	
Optional Stool Questionnaire to accompany Optional Stool sample collection for Correlative Studies[17]			X	X	X	X	X	
Cabozantinib[18]			X	X	X	X		
Pembrolizumab[19]			X	X	X	X		
Survival Follow Up								X[21]

1. Screening procedures must be completed within 28 days prior to C1D1 ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 14 days prior to study treatment.
2. Labs on C1D1 do not need to be repeated if conducted within 14 days of start of treatment
3. Physical Exam including oral examination
4. Hepatitis screening will be performed at screening if clinically indicated.
5. Hematology includes CBC with differential and platelets (must be completed within 2 weeks prior to study enrollment).
6. Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen, phosphorus and magnesium (must be completed within 14 days prior to study enrollment at screening)
7. Additional Labs: Lactate Dehydrogenase, Lipase, Lipid Panel, Gamma Glutamyl Transferase, and should be collected at baseline and at every 4th cycle.
8. Urinalysis including urine protein/creatinine ratio on day 1 of each cycle. Both spot protein/creatinine and the 24 protein/creatinine evaluations are acceptable.
9. Coagulation labs to be collected: PT/INR, APTT. Coagulation panel will only be required at EOT if patients are on active anticoagulant therapy and require monitoring.
10. Free T4, Free T3 and TSH must be performed at baseline ant at least every 4th cycle during treatment
11. Pregnancy test (serum or urine- if urine is positive it must be confirmed with serum test) must be done at screening for all women of childbearing potential and every even cycle (2,4,6 …etc.) during treatment (must be completed within 72hr prior to study enrollment)
12. ECG should be collected at screening (see section 9 for QTcF eligibility details at screening) and at every 4th cycle.
13. CT scans of chest, abdomen and pelvis will be repeated every 4th cycle during treatment within 1 week prior to the corresponding cycle (e.g., prior to cycle 5, 9, 13... etc.). However, if the study treatment is delayed, scans can be delayed to correspond to the treatment schedule, and this will not be a deviation. CT scans will be done at the end of treatment visit only if patient has come off for reasons other than progression. Use of contrast according to institutional practice is recommended but not required.
14. Bone Scans if clinically indicated for evaluation of bone metastatic disease
15. For participants who opt in to the optional tissue collection, tissue may be collected at pre-screening from an urothelial carcinoma diagnostic procedure (soft tissue biopsy or TURBT) or during screening from a soft tissue biopsy (only for patients who do not sign the pre-screening ICF). Subjects are also offered the option of a fresh soft-tissue biopsy or TURBT again prior to treatment at cycle 4 or after. See Section 14 for details.
16. For participants who opt in to the optional blood collection, blood may be collected on C1D1, C2D1, C4D1, C7D1, C13D1, and at end of treatment. See Section 14 for details.
17. For participants who opt in to the optional stool collection, stool may be collected and stool questionnaire administered within 3 days prior to treatment on C1D1, C2D1, C4D1, C7D1, C13D1, and at end of treatment. See Section 14 for details.
18. Cabozantinib at dose specified in dose escalation and specified in section 6.2. Subjects will complete dosing diary for each cycle (Appendix I)
19. Pembrolizumab 200 mg IV q3weeks
20. End of treatment visit should occur within 28 (±14) days after subject completes study treatment
21. Follow up visits: Patients will be followed via telephone contact or medical record review for survival 6 months after completing study treatment. Patients removed from therapy without evidence of progression will undergo radiological examination every 12 (±1) weeks or earlier, if clinically warranted.
22. B type Natriuretic Peptide should be collected
23. Pre-screening ICF and eligibility review must be completed with 4 weeks prior to urothelial carcinoma diagnostic procedure (soft tissue biopsy or TURBT).

9 STUDY PROCEDURES

9.1 Pre-Screening

Pre-screening informed consent

Pre-screening eligibility review

Optional tissue collection (at the time of the standard of care urothelial carcinoma diagnostic procedure) within 4 weeks of study registration

9.2 Screening

Informed Consent

Physical exam

Vital Signs (incl. height/weight)

Review of medical history/baseline symptoms/smoking history/concomitant medications

ECOG Performance status

Labs:

- CBC w/diff
- CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen, phosphorous and magnesium.
- Additional Labs: LDH, Lipase, Lipid Panel, Gamma Glutamyl Transferase, B-type Natriuretic peptide
- Coagulation – PT/INR, APTT
- Thyroid function – TSH, Free T4, Free T3
- Serum pregnancy test (for women of childbearing potential)
- Urinalysis including urine protein creatinine ratio
- Viral Hepatitis Screening (if clinically indicated)

ECG: 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.

CT scans of chest/abdomen/pelvis

Bone Scans if clinically indicated

Optional Tissue Collection for correlatives see section 14

9.3 <u>On-Treatment Evaluations</u>

Physical Exam – **at each cycle**

ECOG Performance Status – **at each cycle**

Vital Signs (Incl. weight) – **at each cycle**

Labs: (do not need to be repeated if screening labs performed within 14 days of C1D1)

- CBC w/diff – **at each cycle**
- CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen, phosphorous and magnesium. – **at each cycle**
- Additional Labs: LDH, Lipase, Lipid Panel, Gamma Glutamyl Transferase, N-type Natriuretic peptide – **at every fourth cycle (4, 8, 12…)**
- Coagulation – PT/INR, APTT – at every fourth cycle (4, 8, 12…)
- Thyroid function – TSH, Free T4, Free T3 – at every fourth cycle (4, 8, 12…)
- Serum pregnancy test (for women of childbearing potential) at every even cycle **(2, 4, 6…)**
- Urinalysis including urine protein creatinine ratio – **at every cycle**

ECG – **at every fourth cycle (4, 8, 12…)**

Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 5.0 – **at each cycle**

Review of concomitant medications – **at each cycle**

CT scans of the chest/abdomen/pelvis and response assessment by RECIST v1.1 to be **repeated every 4th cycle**. However, if the study treatment is delayed, scans can be delayed to correspond to the treatment schedule, and this will not be a deviation.

Bone Scans if clinically indicated

Optional Tissue Collection for correlatives at **cycle 4**, or after, see section 14

Optional Blood and Stool Collection and administration of Stool Questionnaire for correlatives – **at C1D1, C2D1, C4D1, C7D1, C13D1** see section 14

Treatment with 200mg pembrolizumab per section 6.3

Treatment with appropriate dose of cabozantinib – review of patient dosing diary per section 6.2

9.4 End of Treatment Assessments (completed 28 days ± 14 days after completion of treatment

Physical exam

Vital Signs

Concomitant medication collection

ECOG Performance status

Labs:

- CBC w/diff
- CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen. Phosphorus and magnesium
- Additional Labs: LDH, Lipase, Lipid Panel, Gamma Glutamyl Transferase, B-type Natriuretic peptide
- Thyroid function – TSH, Free T4, Free T3
- PT/INR, aPTT if patients are on active anticoagulant therapy and require monitoring
- B-type Natriuretic peptide
- Urinalysis including urine protein creatinine ratio

Optional Blood and Stool Collection and administration of Stool Questionnaire for correlatives see section 14

Adverse event collection for 30 days

CT scans of the chest/abdomen/pelvis and response assessment by RECIST v1.1 to be performed at the end of treatment visit only if patient has come off for reasons other than progression

9.5 Follow-up Assessments

Patients will be followed for 6 months after cessation of study treatment for survival.

Patients removed from therapy without evidence of progression will undergo radiological examination every 12 weeks or earlier, if clinically warranted.

Patients will be followed for SAEs for 90 days after the cessation of treatment

10 CRITERIA FOR EVALUATION AND ENDPOINT

10.1 Efficacy

The primary objective is ORR with a secondary objective of PFS6. Evaluable subjects will be all patients who complete at least one set of disease assessment scans after starting protocol treatment. Patients who discontinue therapy due to clinical progression will also be considered evaluable even if they do not have a set of disease assessment scans.

Patients who discontinue treatment prior to one disease assessment evaluation will be deemed unevaluable and need to be replaced except if the patient was determined to have clinical progression as the reason for discontinuation of therapy. Disease assessments will be measured by CT or MRI scan. All evaluations and treatment decisions will be based on RECIST v1.1 criteria.[28, 29] The iRECIST criteria[30] will be used as an exploratory measurement of efficacy which may be performed retrospectively.

10.1.1 RECIST v1.1

Responses for Phase II patients must be confirmed as follows:

- Partial or complete responses (PR or CR, respectively) must be confirmed by repeat imaging performed 4 to 6 weeks after the first assessment showing PR/CR.
- Stable disease (SD), measurements must have met the SD criteria at least once after study entry at a minimum interval of 9 weeks.
- Patients with progressive disease (PD) who are receiving clinical benefit in the opinion of the investigator will be allowed to continue on treatment after the first evidence of PD. Repeat imaging to confirm PD should be performed according to the schedule of events (9 weeks after the scan showing first evidence of progression) or sooner at the discretion of the investigator but at least 4 weeks after the first evidence of progression.
- Patients who are experiencing unequivocal RECIST v1.1 disease progression or who are not receiving clinical benefit in the opinion of the investigator will not require repeat imaging.

10.1.2 Evaluation of Best Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Target Lesions	Non-Target Lesions	Evaluation of New Lesions	Best Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator. All patients who receive at least one dose of any of the two agents are evaluable for safety.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

11 STATISTICAL CONSIDERATIONS

11.1 Primary objective

This is a non-randomized phase II trial designed to evaluate the combination of pembrolizumab plus cabozantinib. Prior clinical trials of first-line gemcitabine-carboplatin in cisplatin-ineligible patients have been performed. One study identified an objective response rate of 36%, with a median progression-free survival of only 4.8 months in 56 treated patients.[23] A second study of 60 patients noted an objective response rate of 38.4%, with a median progression-free survival of 7.6 months. [24] It has also been reported a 26% ORR in patient treated with pembrolizumab with locally advanced or metastatic urothelial cancer[25]. ORR will be analyzed descriptively. The proportion of objective responses will be reported and a 95% one-sided exact binomial confidence interval (Clopper-Pearson) will be calculated for ORR. With 35 evaluable subjects the lower bound of the 95% confidence interval will extend no more than 26% from the observed proportion. If there are 17 or more objective responses in 35 patients the confidence interval will exclude 32%. Adding another 10% for unevaluable patients that may be enrolled, a total of up to 39 patients will be enrolled.

11.2 Secondary Objectives and Endpoints

The secondary objectives are to evaluate progression free survival at 6 months and overall survival of pembrolizumab + cabozantinib in subjects with UC. Kaplan-Meier methods and associated confidence intervals will be used to analyze PFS and OS. Subjects will be evaluated for survival for 6 months or until death after discontinuation of study treatment. The proportion of subjects who exhibit an objective response will be reported along with an exact binomial confidence interval. As an additional secondary analysis, stratified Kaplan-Meier methodology will be used to associate risk group (based on performance status and visceral metastasis) with PFS.

11.3 Exploratory Objectives and Endpoints

We are planning to evaluate molecular markers of tissue in tissues to correlate with response to drug treatment and blood markers to evaluate pharmacodynamic markers of drug mechanisms. However, the specific biomarker tests and assays have not yet been finalized. Once a decision has been made, a statistical plan will be written and an amendment to the protocol will be made.

12 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Correlative Studies

Correlative studies may include but are not limited to analysis that identify the mechanisms of response and resistance to immunotherapy, at the cellular and molecular levels.

14.1.1 Collection of Tumor Tissue

Participants who opt in to the optional tissue collection, tissue may be collected at pre-screening from an urothelial carcinoma diagnostic procedure (soft tissue biopsy or TURBT) or during screening from a soft tissue biopsy (only for patients who do not sign the pre-screening ICF). Subjects are also offered the option of a fresh soft-tissue biopsy or TURBT again prior to treatment at cycle 4 or after. Up to ten sections will be collected during the TURBT and up to six cores will be obtained at the time of soft tissue biopsy. These tissues will be used to establish a biomarker panel predictive of treatment efficacy which will be validated in future clinical trials.

Testing may include, but is not limited to:

- Multiomics platforms
- Immunohistochemistry
- Flow cytometry
- Ex vivo treatment to predict treatment efficacy

Instructions for processing and analysis will be detailed in the lab manual.

14.1.2 Collection of Blood for Correlative Analysis

Participants who opt in to the optional blood collection, up to 36mL of blood may be collected on C1D1, C2D1, C4D1, C7D1, C13D1, and at end of treatment.

These samples will be used to test for biomarkers of disease response and prediction of treatment effect. Testing may include, but is not limited to:

- C-reactive protein (CRP)
- Neutrophil to Lymphocyte ratio
- Hemoglobin
- Cytokine/chemokine/interferon assays
- Flow cytometry
- Mass cytometry
- T-cell kinetics
- Genome analysis

Specimen collection and processing instructions can be found in the lab manual.

14.1.3 Collection of Stool Samples for Correlative Analysis

Collection of stool samples and administration of Stool Questionnaire may occur prior to treatment on cycles 1, 2, 4, 7, 13, and at the end of treatment. Stool collection kits will be given to subjects at the clinic visit preceding the collection time point and they will be instructed to collect the sample within 3 days prior to the time points noted above and answer the questionnaire provided in the stool kit (Appendix B).

These samples will be used to determine a predictive microbiome signature associated with therapeutic response.

Testing may include, but is not limited to:

- 16S ribosomal RNA sequencing
- Cultivation of microbes
- Shotgun metagenomics

Specimen collection and storage instructions can be found in the lab manual and the patient stool collection instructions.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II, multicenter, study classified as high risk per the NCI-approved DSM plan.

Each high risk study may be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Approval of the medical monitor is required for all dose escalations. SAEs occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment and within 30 days of their last treatment on a quarterly basis.

Each high-risk study will be assigned a dedicated research compliance officer who will monitor the trial. High-risk trials will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that

increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

A safety analysis will be performed after the first 6 patients enroll and receive treatment. During this stage, the decision to continue enrollment will be made by the Data Safety and monitoring committee (DSMC). When all 6 subjects in the have been followed for at least 21 days following first dose of pembrolizumab and cabozantinib, all available safety data will be considered in a decision to continue enrollment.

15.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

15.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The collection of adverse events will begin after the signature of the consent form and end 30 days post the last dose of study treatment.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

Adverse events should be evaluated to determine:

1. The severity grade based on CTCAE v.5.0 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related).
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 7 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drugs is described in the Drug Information (section 3) and (the most recent Investigator Brochures). This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.4.2 **Serious Adverse Event (SAE)**

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Serious adverse event collection will begin after the signature of the consent form and end 90 days after the last dose of study treatment or until new cancer treatment is initiated, if sooner.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

15.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Exelixis according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of event. Medwatch 3500A form can be downloaded from the FDA website.

DSMC Notifications:

An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for this study.

The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

FDA Notifications:

Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational drug

Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.

- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

Events meeting the University of Utah IRB or local IRB reporting requirements will be submitted per local guidelines.

Drug Manufacturer Notifications:

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

15.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

15.7 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.

15.8 Protocol Amendments

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation. Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

15.9 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.10 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

15.11 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.12 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified. Additional monitoring of the study documentation and record keeping can be monitored by Exelixis according to the clinical trial agreement.

16 PUBLICATIONS OF DATA

The Principal Investigator 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 in accordance with the clinical trial agreement.

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APPENDIX A - Cabozantinib Dosing Diary

Patient Instructions:

1) Take the number of pills prescribed to you by your study doctor each day with an 8oz glass of water at approximately the same time each day.
2) If a pill is forgotten, it may be taken as soon as you remember on the same day with a return to normal scheduling the following day.
3) Do not take 2 doses of Cabozantinib on the same day to try and make up for a missed dose.
4) Complete one line of the diary each day and write the total number of pills taken each day. If a dose is missed, indicate "dose not taken", in the comments briefly explain why, especially noting whether this is a dose reduction to every other day administration.
5) Please bring this diary as well as all empty containers and any unused supplies to your next clinic visit.

Day	Date	Time	Number of Pills Taken	Comments
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

Patient Signature _____ Date_____

APPENDIX B- Stool Sample Collection Questionnaire

Stool Collection Questionnaire

Date Collected:

Time Collected:

Dietary Questionnaire

In the last week:

How often did you consume red meat?

Never ☐ Once ☐ 2 – 5 times ☐ Daily ☐

How often did you consume desserts, sweets, soda, or juice?

Never ☐ Once ☐ 2 – 5 times ☐ Daily ☐

How often did you consume high fiber foods?

Fresh vegetables? Never ☐ Once ☐ 2 – 5 times ☐ Daily ☐
Whole grains*? Never ☐ Once ☐ 2 – 5 times ☐ Daily ☐
Fresh Fruit? Never ☐ Once ☐ 2 – 5 times ☐ Daily ☐

**Examples include oatmeal, quinoa, brown/wild rice, barley, whole-wheat products.*

For the use of the Huntsman Cancer Institute, study coordinator

Time-point:
Study ID:
Study Name: