FRED HUTCHINSON CANCER CENTER UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

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Title of Protocol:
A Phase 2 trial of cabozantinib and pembrolizumab in the first-line treatment of advanced hepatocellular carcinoma

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A Phase 2 trial of cabozantinib and pembrolizumab in the first-line treatment of advanced hepatocellular carcinoma

PROJECT SYNOPSIS

Title	A Phase 2 trial of cabozantinib and pembrolizumab in the first-line treatment of advanced hepatocellular carcinoma
Version date	August 11, 2021
Study center	University of Washington/Fred Hutchinson Cancer Center
Number of subjects	29 patients
Study duration	Accrual period: 24 months; follow-up period: 12 months
Background and rationale	Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related mortality globally. Prognosis is poor for patients with advanced disease despite the recent approval of several new agents. The immune system plays a critical role in the pathogenesis of HCC. Increased regulatory T cells, decreased CD8+ and CD4+ tumor-infiltrating lymphocytes, and high PD-1/PD-L1 expression are associated with poorer outcomes. This is supported by the efficacy of PD-1 inhibitors currently approved in the second-line treatment of HCC, after progression on VEGFR tyrosine kinase inhibitors. Promising early results were noted for combinations of immune checkpoint inhibitors and VEGF/VEGFR blockade, which may activate synergistic or inhibit resistance pathways. Lenvatinib and pembrolizumab led to an ORR of 42%, while bevacizumab and atezolizumab led to an ORR of 61% in the first-line treatment of advanced HCC. Furthermore, the role of cMET signaling is increasingly recognized in HCC. Cabozantinib is a multikinase inhibitor against cMET, VEGFR1-3 and AXL. The Phase 3 CELESTIAL trial demonstrated a significant improvement in OS with cabozantinib compared to placebo in patients post-sorafenib (HR 0.76, 95% CI 0.63-0.92, p=0.0049), leading to FDA approval for patients with advanced HCC previously treated with sorafenib. Evidence also supports the immunomodulatory effects of cMET and the TAM receptors including AXL via enhancement of PD-L1/PD-L2 expression and regulation of immune effector and regulatory cells, thus supporting a combination strategy with cabozantinib and immunotherapy. There is a strong rationale for the combined inhibition of c-MET/VEGFR and PD-1 in HCC. This Phase 2 clinical trial will evaluate the efficacy of cabozantinib and pembrolizumab in the first-line treatment of patients with advanced HCC.
Design	Non-randomized Phase 2 trial (Simon's optimal two-stage design)
Objectives	**Primary objective** • To determine the objective response rate (ORR) of the combination of

	cabozantinib and pembrolizumab in the first-line treatment of advanced HCC based on RECIST v1.1. **Secondary objectives** • To assess the disease control rate (DCR) by RECIST v1.1, ORR and DCR by iRECIST, progression-free survival (PFS) by RECIST v1.1, and overall survival (OS). • To assess the safety of the combination of cabozantinib and pembrolizumab based on NCI CTCAE v5. **Exploratory objectives** • To explore the predictive biomarkers for cabozantinib and pembrolizumab in HCC in blood and archival tissue or pre-treatment fresh tumor biopsy (if applicable).
Inclusion and exclusion criteria	**Inclusion criteria** 1. At least 18 years of age. 2. Must have a histologically confirmed diagnosis of HCC or a non-invasive diagnosis of HCC as per the American Association for the Study of Liver Diseases (AASLD) criteria. a. If available, archival tissue must be submitted. b. Mixed HCC-cholangiocarcinoma is not allowed. 3. Patient has BCLC stage C disease, or BCLC stage B disease that is not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to curative treatment. a. Previous locoregional therapy is allowed (e.g. surgical resection, external beam radiation, catheter-based therapy), and patients must have evidence of disease progression from locoregional therapy. 4. Must have measurable disease by RECIST v1.1. a. Lesions that were previously radiated or ablated cannot be target lesions unless there was subsequent radiographic progression at those sites. 5. No prior systemic therapy for HCC. Prior chemotherapy given locally into the liver (e.g. TACE) is allowed. 6. Must have Child-Pugh class A hepatic function within 7 days prior to first dose of study intervention (Appendix 6). 7. ECOG performance status 0-1 (Appendix 5). 8. Life expectancy of at least 12 weeks. 9. Recovery to baseline or ≤ Grade 1 toxicities (CTCAE v5) related to any prior treatments, unless adverse events (AEs) are clinically nonsignificant and/or stable on supportive therapy. 10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment: a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 without granulocyte colony-stimulating factor support. b. Platelets ≥ 60,000/mm^3 without transfusion within 14 days.

c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion or EPO dependency within 14 days.
d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN).
e. Total bilirubin ≤ 2 mg/dL OR direct bilirubin ≤ ULN for participants with total bilirubin levels >2 mg/dL.
f. Serum albumin ≥ 2.8 g/dl (≥ 28 g/L) without albumin infusion.
g. Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≤ 1.5 × ULN.
h. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation (Appendix 7).
i. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) or 24h urine protein ≤ 1g.
j. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization or fasting serum glucose ≤ 160 mg/dL.

11. Patients with positive hepatitis B surface antigen (HBsAg) and/or HBV viral load >100 IU/mL at the time of enrollment are eligible to enroll on study if they meet the following criteria:
    a. Anti-HBV therapy as per institutional practice must be given at least 4 weeks and HBV viral load must be <100 IU/mL prior to initiating study treatment. Patients on active HBV therapy with viral loads <100 IU/mL should remain on the same therapy throughout study treatment.
    b. Note: Patients with positive anti-hepatitis B core antibody (HBcAb), negative HBsAg, and negative or positive anti-hepatitis B surface antibody, and who have an HBV viral load <100 IU/mL do not require anti-viral prophylaxis.
12. Patients with past or ongoing hepatitis C infection (HCV) are eligible to enroll on study, with or without prior anti-viral treatment, as long as the other eligibility criteria are met. Treated patients must have completed their anti-viral treatment at least 1 month prior to initiating study treatment.
13. Sexually active fertile subjects and their partners must agree to use effective methods of contraception (see Appendix 8) during the course of the study and for at least 4 months after the last dose cabozantinib. They must also refrain from donating sperm during this time period.
14. Female subjects of childbearing potential must not be pregnant at screening and not breastfeeding. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e. females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy).
    a. Women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.
15. Capable of understanding and complying with the protocol requirements and must provide written informed consent/assent for the study.

Exclusion criteria

	1. Prior treatment with any systemic therapy for HCC, including anti-VEGF therapy or any systemic investigational agent. a. If the patient previously received systemic treatment for reasons other than HCC: small molecule kinase inhibitors are not allowed within 2 weeks and cytotoxic/biologic agents are not allowed within 4 weeks of study treatment. 2. Prior exposure to immune checkpoint inhibitors or other immunotherapeutic agents. 3. Currently participating in or has participated in a study of an investigational agent or device within 4 weeks prior to the first dose of study treatment. 4. Major surgery within 6 weeks or minor surgery (e.g. dental extraction) within 10 days prior to first dose of study treatment. a. Complete wound healing from major surgery must have occurred at least 1 month before first dose and from minor surgery (e.g. simple excision, tooth extraction) at least 7 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible. 5. Local liver-directed therapy within 4 weeks of initiating study treatment. 6. Palliative radiation for the purpose of symptomatic relief to non-liver and non-CNS disease within 2 weeks of starting treatment. Other radiation treatments within 4 weeks of starting treatment. a. Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and have not had radiation pneumonitis. 7. Prior liver or other allogenic tissue/organ transplantation. 8. History of primary immunodeficiency. 9. Active autoimmune or inflammatory disease that has required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). This includes, but is not limited to, inflammatory bowel disease, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, Graves' disease, etc. a. The following autoimmune conditions are allowed: vitiligo or alopecia; hypothyroidism on stable hormone replacement therapy; psoriasis/eczema not requiring systemic treatment. b. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed. 10. Chronic use of systemic steroid (in dosing exceeding 10 mg daily of prednisone equivalent) or immunosuppressive therapy or use within 14 days prior to enrollment. a. The following treatments are allowed: intranasal, inhaled, topical or local steroid injections; systemic corticosteroids at physiologic doses equivalent to no more than prednisone 10 mg/day; steroids as premedication for contrast dye allergy. 11. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. 12. History of hepatic encephalopathy or treatment to prevent or control

encephalopathy within the past 12 months. Subjects on lactulose and/or rifaximin to control hepatic encephalopathy are not allowed.

13. Esophageal or gastric variceal bleeding within the past 6 months. All subjects will be screened for esophageal varices unless performed in the last 6 months before study treatment. If varices are present, they should be treated according to institutional standards before starting study treatment.
14. Uncontrolled ascites, clinically significant or symptomatic ascites requiring paracenteses or increasing doses of diuretics within the past 3 months.
    a. Patients who are on stable diuretic doses for at least 3 months are eligible if they meet other eligibility criteria.
    b. Asymptomatic ascites detected on imaging are allowed.
15. Has known history or any evidence of CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are asymptomatic and radiologically stable (i.e. without progression for at least 4 weeks by repeat imaging (which must be performed during study screening), clinically stable, and without the need steroids for at least 4 weeks prior to first dose of study treatment).
16. Concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g. clopidogrel). Allowed anticoagulants are the following:
    a. Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
    b. Low molecular weight heparin (LMWH) is permitted.
    c. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 4 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
17. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias with risk of hemodynamic instability within 12 months before the first dose of study treatment.
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 95 mm Hg diastolic despite optimal antihypertensive treatment, and/or change in antihypertensive medications within 1 week before starting treatment. Note: eligibility of a subject receiving 4 or more antihypertensive medications prior to study entry will require approval from the PI.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or arterial thromboembolic within 12 months before the first dose.
        iv. Asymptomatic venous thromboembolic event (e.g. deep venous

	thrombosis, pulmonary embolism) is allowed if the patient has been stable on anticoagulation with LMWH for at least 4 weeks. b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation: i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g. Crohn's disease), GI malabsorption, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction. ii. 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. c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, other history of significant bleeding (e.g. pulmonary hemorrhage) within 12 weeks before first dose, or known thrombotic disorder. d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation. e. Lesions invading any major blood vessels, including inferior vena cava or cardiac involvement of HCC based on imaging. Note: Main and branch portal vein and hepatic vein invasion is allowed. f. Ongoing active infection requiring antibiotics. Antibiotics must be completed at least 7 days before initiating study treatment. g. Known active tuberculosis. h. Serious non-healing wound, ulcer, or bone fracture. 18. Patients with proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 hours will be ineligible. 19. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (EKG) within 28 days before first dose of study treatment. a. Note: If a single EKG shows a QTcF with an absolute value > 500 ms, two additional EKGs at intervals of approximately 3 min must be performed within 30 min after the initial EKG, and the average of these three consecutive results for QTcF will be used to determine eligibility. 20. Inability to swallow tablets or any other condition that might interfere with oral absorption of medications. 21. Previously identified allergy or hypersensitivity to study drugs and/or any of their excipients. 22. Ongoing secondary malignancy that is progressing and/or has required active treatment within the past year. Adjuvant treatment for resected breast cancer is allowed. a. Subjects with basal cell carcinoma of the skin, squamous cell carcinoma or the skin, prostate cancer, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are allowed.

	23. Has a known history of HIV infection. Note: HIV testing is not mandated for screening. 24. Co-infection with HBV (HBsAg (+) and /or detectable HBV DNA) and HCV (anti-HCV Ab (+) and detectable HCV RNA) at study entry. 25. Co-infection with HBV and HDV at study entry. 26. Live vaccine or live attenuated vaccine within 30 days prior to first dose of study treatment. Administration of killed vaccines is allowed. 27. Pregnant or lactating females. 28. Known psychiatric illness, substance abuse disorder, or other condition that would interfere with the ability to comply with the requirements of the study. 29. Has history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
Study treatments	All enrolled patients will receive cabozantinib 40mg PO daily continuously and pembrolizumab 200mg IV every 3 weeks, in 3-week cycles. Dose modifications of cabozantinib and/or pembrolizumab may be made for adverse events (AEs) (guidelines provided in protocol). Immune-related AEs will be treated per published guidelines. If one agent needs to be discontinued due to treatment-related toxicity, patients may continue to receive treatment with the other agent. Treatment will continue until disease progression, intolerance, or patient withdrawal. Treatment beyond progression will be allowed if pre-specified criteria are met (Section 12.1).
Study assessments	Toxicity assessments (history, physical exam, labs) will occur weekly during cycle 1, then every 3 weeks on day 1 of each subsequent cycle. AEs will be graded by NCI CTCAE v5. Disease assessments will be performed by multiphasic contrast CT or MRI of abdomen/pelvis, as well as CT chest with or without contrast at baseline (within one month of enrollment) and every 9 weeks on treatment. Tumor response will be determined by RECIST v1.1 and iRECIST. The tumor marker alpha-fetoprotein (AFP) will also be measured at baseline and every 9 weeks if abnormal at baseline. If patients discontinue treatment due to intolerable or unacceptable toxicity, they will be followed for progression and for survival at least every 4 months up to 3 years.
Statistical plan and sample size calculation	This Phase 2 trial uses Simon's optimal two-stage design. The null hypothesis that the true ORR by RECIST v1.1 is 20% will be tested against a one-sided alternative that the assumed-true ORR with the tested combination is 38%. In the first stage, 13 patients will be accrued. If there are 2 or fewer patients with

	response (an observed ORR of 15% or less), the study will be suspended for lack of sufficient efficacy. Otherwise, 16 additional patients will be accrued for a total of 29 patients. The null hypothesis (ORR 20%) will be rejected if 9 or more patients have a tumor response out of 29 patients (an observed ORR of at least 31%). This design yields a type I error rate of 0.10 and power of 80% when the true ORR is 38%.
Anticipated findings	It is anticipated that the combination of cabozantinib and pembrolizumab will significantly improve the ORR of patients with advanced HCC in the first-line treatment setting.

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1.0 INTRODUCTION

1.1 Overview of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and is the 5th most common cancer (estimated 841,080 incident cases in 2018 worldwide) and the 3rd leading cause of cancer-related mortality globally (estimated 781,631 deaths in 2018 worldwide).[1,2] Men are 3.5 times more likely than women to develop HCC. The rate of HCC has risen significantly in the US in the last decade with an annual increase in incidence of 3.64% based on analysis of the SEER data from 2000-2012.[3] Moreover, this trend is projected to continue into the next decade with aging of the baby boomers. It is estimated that the incidence rate (per 100,000 person-years) of HCC in adults will increase from 13.5 in 2013 to 17.0 in 2020 and 21.2 in 2030.[3]

Common etiologic factors for HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, metabolic disorders (e.g. obesity, non-alcoholic fatty liver disease, diabetes), and smoking.[4] HBV is the most important etiology of HCC worldwide and accounts for >50% of cases, mainly in HBV-endemic parts of southeast Asia and Africa.[5] In the US, HCV, alcohol, and increasingly metabolic disorders are the primary risk factors for HCC.[6]

HCC is associated with poor prognosis. The 5-year overall survival (OS) of patients with primary liver malignancy is estimated to be 18%.[7] The median OS of patients with advanced HCC remains limited (~18 months) despite recent developments in systemic therapy.[8] Thus, there is an ongoing need to develop novel therapeutic strategies in this disease.

1.2 Systemic therapy in advanced HCC

1.2.1 Approved targeted multikinase inhibitors

Sorafenib has specificity for RAF, VEGFR1-3 and PDGFRb, and was the first agent to significantly improve OS compared to placebo in patients with advanced HCC as demonstrated by the Phase 3 SHARP trial, serving as a standard treatment since 2007.[9] Recently, several similar multikinase inhibitors with targets including VEGFR, PDGFR, FGFR and other receptors have been approved. In the REFLECT trial, lenvatinib was non-inferior to sorafenib with respect to OS and is now an additional first-line therapy option.[10] The data also demonstrated that achieving an objective response was an independent predictive factor for increased OS.[11]

In the RESORCE trial, regorafenib significantly improved OS compared to placebo (10.6 vs. 7.8 months; HR 0.63, 95% CI 0.50-0.79, p<0.0001) in advanced HCC patients who progressed on and tolerated prior sorafenib.[12] Anti-tumor activity of these multikinase inhibitors comes from their anti-angiogenic, anti-proliferative, and pro-apoptotic effects.

1.2.2 MET inhibition and cabozantinib

The importance of the MET receptor signaling pathway, which is activated by its ligand HGF, is increasingly recognized in HCC. MET overexpression is observed in a large subset of HCC tumors and is associated with poorer survival.[13,14] MET activation and signaling mediates the epithelial-to-mesenchymal transition,

invasion, and tumor metastasis.[15] In fact, the anti-tumor activity of MET inhibition in HCC has been well established in both preclinical and early clinical studies.[16,17] Particularly, MET activation is believed to be one of the mechanisms of resistance to anti-VEGF therapy, providing the rationale for concurrently inhibiting VEGFR and MET.[18,19]

Cabozantinib is a multikinase inhibitor with its primary activity against MET, VEGFR1-3 and AXL.[20] The Phase 3 CELESTIAL trial randomized (2:1) patients with advanced HCC who previously progressed on sorafenib to cabozantinb 60mg orally daily vs. placebo. Cabozantinib demonstrated a significant improvement in OS (10.2 vs. 8.0 months, HR 0.76 (95% CI 0.63-0.92), p=0.005) and in PFS (5.2 vs. 1.9 months, HR 0.44 (95% CI 0.36-0.52), p<0.001) compared to placebo. The objective response rate (ORR) was 4% vs. < 1% (p=0.009).[21] In this trial, 68% of patients experienced a grade 3 or 4 AE (vs. 37% in patients receiving placebo). In the cabozantinib arm, dose reduction was required in 62% of patients, while 16% of patients discontinued treatment due to toxicity. Moreover, the median daily dose of cabozantinib received was 35.8 mg daily.

Based on results of the CELESTIAL trial, cabozantinib was FDA approved for the treatment of advanced HCC post-sorafenib in January 2019.

1.2.3 Immuno-modulation by the PD-1 pathway

The programmed cell death 1 (PD-1) receptor is essential in the control of the immune system. It is expressed on surface of activated lymphocytes including CD4+ and CD8+ T cells, B cells, T regulatory cells, and natural killer cells. The ligands for PD-1 are PD-L1 and PD-L2, which are expressed or induced in various cell types. Binding of PD-L1 or PD-L2 to PD-1 inhibits T cell activation, therefore modulating immune responses to prevent autoimmune reactions. PD-L1 expression can be found in the vascular endothelium and other non-hematopoietic tissues, while PD-L2 is mainly expressed on antigen-presenting cells.[22,23]

PD-L1 expression occurs at low levels in normal tissues. However, many cancers express high levels of PD-L1 in order to inhibit T cell activation and anti-tumor immune responses.[24] Thus, immune checkpoint inhibition of the PD-1 pathway is one therapeutic strategy to prevent suppression of T cell responses against tumor cells.

1.2.4 Immune checkpoint inhibition in HCC

The immune system plays a critical role in the pathogenesis of HCC.[25] The cirrhotic liver is marked by an immunosuppressive state.[26] Increased T regulatory cells, decreased CD8+ or CD4+ T cells, and high PD-L1/PD-L2 expression are associated with disease progression and poorer outcomes.[27-33]

Immune checkpoint inhibition has been shown to be an active therapeutic strategy in this disease. In the Phase 1/2 trial CheckMate 040 of nivolumab in patients with advanced HCC with or without prior sorafenib, the ORR by modified RECIST (mRECIST) was 20% (95% CI 15-26) in the dose-expansion phase, while the 6- and 9-month OS was 83% (95% CI 78-88) and 74% (95% CI 67-79), respectively.[34] Response was observed independent of PD-L1 expression and HCC etiology. Likewise, in the Phase 2 trial KEYNOTE-224, patients with advanced HCC who progressed on sorafenib were treated with pembrolizumab and demonstrated an ORR of 17% (95% CI 11-26) and a disease control rate (DCR) of 62% (95% CI 52-71) by mRECIST.[35] Both nivolumab and pembrolizumab were safe and tolerable; the rate of grade 3 or 4 treatment-related adverse events (TRAEs) was 25% with both agents. Efficacy and toxicity were both independent of viral infection status. [34,35] Subgroup analyses suggested greater response in tumors with

PD-L1 overexpression by the combined positive score, although further validation studies are needed. Interestingly, the randomized Phase 3 trial KEYNOTE-240 of pembrolizumab vs. best supportive care in patients with advanced HCC previously treated with sorafenib did not meet its primary endpoints of OS and PFS.[36] However, the study had a stringent pre-specified p-value cutoff of 0.0174 for statistical significance, and there was a clear trend towards improved OS with pembrolizumab compared to best supportive care (median OS 13.9 vs. 10.6 months, HR 0.781 (95% CI 0.611-0.988), p=0.0238). Subsequent therapies received by the two groups also likely affected the results. Similar to prior experience, the ORR with pembrolizumab was 18.3% (95% CI 14.0-23.4).[36]

Moreover, PD-1 inhibition has been evaluated in the first-line treatment setting in HCC patients in the CheckMate 459 trial of nivolumab vs. sorafenib. The trial did not meet its primary endpoint of OS, with a median OS of 16.4 vs. 14.7 months (HR 0.85 (95% CI 0.72-1.02), p=0.0752). ORR was 15% vs. 7%. Subsequent therapies received might have affected the OS, as 38% and 46% of patients in the nivolumab and sorafenib arms, respectively, received subsequent treatments.[37]

Nivolumab and pembrolizumab are currently approved for the second-line treatment of advanced HCC. Other immune checkpoint inhibitors currently in development in HCC include anti-PD-L1 (e.g. durvalumab, atezolizumab) and anti-CTLA4 (e.g. tremelimumab) agents.

1.2.5 Combination therapy with immune checkpoint inhibitors in HCC

The ORR associated with nivolumab and pembrolizumab monotherapy in refractory HCC was 20% and 17%, respectively.[34,35] Thus, there is a need to improve on these outcomes and maximize the efficacy of immune checkpoint inhibitors. Combination approaches have been explored and yielded promising early results.

There is now growing evidence for the combination of VEGF/VEGFR-targeting agents and PD-1/PD-L1 inhibition, which may lead to increased effector T cell infiltration into tumors.[38]

The combination of lenvatinib and pembrolizumab was evaluated in a Phase 1b trial of HCC patients in the first-line treatment setting. There were 6 patients in the DLT evaluation phase (Part 1) and 24 patients in the expansion phase (Part 2). This study demonstrated an ORR of 42% (95%CI 23-63) by mRECIST criteria (complete response (CR) 4%, partial response (PR) 39%).[38] The median progression-free survival (PFS) was 9.69 (95%CI 5.55-NE) months. The rate of grade 3-4 treatment-emergent adverse events (TEAEs) was 60%, and the rate of serious adverse events (SAEs) was 27%, including 3 deaths (out of 30 patients). The most common TEAEs were: decreased appetite (53%), hypertension (53%), diarrhea (43%), fatigue (40%), dysphonia (30%), proteinuria (30%), AST elevation (27%), weight loss (27%), hypothyroidism (20%), nausea (20%), and palmar-plantar erythrodyesthesia syndrome (PPES) (20%). The most common grade 3 TEAEs were: hypertension (17%), AST elevation (17%), decreased WBC (13%), hyponatremia (10%). 60% of patients required dose interruption of lenvatinib or pembrolizumab due to a TEAE, and 60% of patients had a dose reduction of lenvatinib. The rate of discontinuation of lenvatinib or pembrolizumab was 17%.[38]

Furthermore, a Phase 1b trial of atezolizumab and bevacizumab was conducted in solid tumors, in which Arms A and F enrolled treatment-naïve patients with unresectable HCC. Arm F was a randomized cohort of atezolizumab/bevacizumab vs. atezolizumab.[39] The combination regimen demonstrated a significant improvement in the primary endpoint of PFS compared to atezolizumab monotherapy (median PFS 5.6 vs. 3.4 months; HR 0.55, 80% CI 0.40-0.74, p=0.0108). TRAEs occurred in 68% in the atezo/bev group (grade 3 TRAEs, 20%) and 41% in the atezo group (grade 3 TRAEs, 5%). In Arm A, 104 patients with

treatment-naïve unresectable HCC received atezolizumab/bevacizumab; its primary endpoint of ORR was 36% (76% of responses were ongoing at the time of data cutoff). There were 88% TRAEs, and 39% grade 3-4 TRAEs (most commonly hypertension).

While these were early phase studies with small numbers of patients, their results provided strong support for combining VEGF blockade with immune checkpoint inhibitors for increased efficacy in HCC. The combination of atezolizumab plus bevacizumab previously received FDA breakthrough designation for development in HCC.[40] In fact, the Phase 3 randomized trial of atezolizumab/bevacizumab vs. sorafenib (IMbrave 150) for the first-line treatment of unresectable HCC met its primary endpoint of OS and PFS (press release October 21, 2019).[41]

Other similar immunotherapy combination Phase 3 trials in treatment-naïve advanced HCC patients are currently ongoing: lenvatinib/pembrolizumab vs. lenvatinib (LEEP-002) (NCT03713593), and cabozantinib/atezolizumab vs. sorafenib vs. cabozantinib (COSMIC-312) (NCT03755791).

1.3 Rationale for combining cabozantinib and pembrolizumab in HCC

Both cabozantinib and pembrolizumab have clinical activity as monotherapy in advanced refractory HCC, and there is significant benefit in combining VEGFR and PD-1 inhibition in the first-line treatment setting, as discussed above. In addition, MET has been shown to play an immunosuppressive role by interacting with immune checkpoint pathways. For instance, MET mediates immune suppression by upregulating PD-L1 expression, while PD-L1 and PD-L2 have been associated with increased levels of MET and VEGF.[42,43] Co-expression of MET and PD-L1/PD-L2 was observed in squamous cell carcinomas of the lung and esophagus.[44,45] Similarly, the TAM family of receptors including AXL have been demonstrated to suppress the immune system. Cabozantinib has specificity against AXL and has been shown to modulate the tumor microenvironment, as well as immune suppressor and effector cells.[46-49]

There is a strong rationale for combining inhibition of MET, AXL/TAM receptors, VEGFR and PD-1 in HCC through the combination of cabozantinb and pembrolizumab, which will be explored in this non-randomized Phase 2 trial in the first-line treatment of patients with advanced HCC.

1.4 Study drug information

1.4.1 Cabozantinib drug profile

Please refer to the Investigator's Brochure for complete information on cabozantinib.

1.4.1.1 Target specificity

Cabozantinib (XL184) is a multikinase targeted agent with specificity against several receptor tyrosine kinases. The main targets are MET (IC50 8 nM), VEGFR2/KDR (IC50 2 nM), and RET (IC50 85 nM), but it also inhibits KIT (IC50 5 nM), FLT3 (IC50 11 nM), and AXL (IC50 42 nM). Based on cellular and in vivo activity assays, cabozantinib exhibits comparable anti-tumor activity against MET and VEGFR2, with lesser activity against RET, KIT, AXL and FLT3.

1.4.1.2 Preclinical data

Preclinical studies demonstrated that cabozantinib given orally effectively blocked the phosphorylation of MET and VEGFR2 in tumor xenograft models, and the duration of inhibition was over 8 hours at 100 mg/kg.[50] In vivo changes in tumor vasculature and apoptosis were observed in xenografts treated with cabozantinib. Moreover, cabozantinib induced significant tumor growth inhibition or regression in xenograft models across various tumor types, including medullary thyroid cancer, breast cancer, lung cancer, and glioblastoma.[50] In a MET-overexpressed HCC xenograft model, cabozantinib prolonged the survival of mice compared to vehicle.[51] There is also evidence that cabozantinib has specific anti-tumor activity in bone metastatic lesions.[50,52]

1.4.1.3 Pharmacokinetics (PK)

A population PK analysis of cabozantinib at 60 mg daily (dose reduction allowed) in patients with renal cell carcinoma showed it had the following characteristics: terminal half-life 99 h, terminal volume of distribution (V/F) ~319 L, clearance at steady state 2.2 L/h. Clearance was independent of age and sex. Cabozantinb is mostly protein-bound in circulation.

Cytochrome P450 and potential interactions with cabozantinib

Data from a clinical drug interaction study (Study XL184-008) showed 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).

Based on in vitro studies, cabozantinib is a CYP3A4 substrate and a weak CYP2C9 substrate (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate). 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 (see Appendix 4) may significantly decrease cabozantinib concentrations. The chronic use of these strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be also used with caution due to the potential decreased exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended if possible.

In addition, 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 (see Appendix 4) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs with inhibitory effects on 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 if possible.

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 of the co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Other interactions

Food may increase exposure levels of cabozantinib by 57%. Therefore, 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. 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.

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 (e.g. PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

1.4.1.4 Clinical safety in clinical trials of cabozantinib

Cabozantinib has been studied across multiple malignancies, including HCC, medullary thyroid, prostate, breast and non-small cell lung cancers, renal cell carcinoma, melanoma, and glioblastoma multiforme.[50] The capsule formulation has been approved in the US for refractory metastatic medullary thyroid cancer, and the tablet formulation has been approved for advanced renal cell carcinoma and HCC.

Please see the Investigator's Brochure for the most updated safety information on cabozantinib. Per Investigator Brochure v13, safety data are available from 2611 subjects who have been dosed with cabozantinib (2453 subjects in single agent cabozantinib studies [2410 subjects in a pooled analysis and 43 subjects in a Japanese study] and 158 subjects in combination studies of cabozantinib with other agents).

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

Other medically important but less frequent AEs included: arterial thrombotic AEs (eg, 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).

AEs 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.

AEs may occur within the first few weeks in the course of treatment with cabozantinib, as the drug is expected to reach steady state exposure at approximately 2 weeks following the first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. AEs should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions/delays should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (see Section 9.0).

1.4.1.5 Safety of cabozantinib in HCC patients

The safety profile of cabozantinib in HCC patients was characterized in a Phase 2 randomized discontinuation study and in a Phase 3 clinical trial.[21,53] CELESTIAL was a Phase 3 randomized trial of cabozantinib (n=470) vs. placebo (n=237) in patients with HCC and Child-Pugh class A5 liver function previously treated with sorafenib. The starting dose of cabozantinib was 60 mg daily, and 62% of patients required dose reductions with a median time to first dose reduction of 38 days. The median average daily dose administered was 35.8 mg daily.

In the CELESTIAL trial, TEAEs occurred in 99% of patients, with grade 3-4 AEs in 68% of patients and SAEs in 50% of patients. The most common TEAEs in >=20% of patients were: diarrhea (54%), decreased appetite (48%), PPES (46%), fatigue (45%), nausea (31%), hypertension (29%), vomiting (26%), AST increased (22%), and asthenia (22%). The most common grade 3-4 TEAEs in >=5% of patients were: PPES (17%), hypertension (16%), AST elevation (12%), diarrhea (10%), fatigue (10%), asthenia (7%), decreased appetite (6%), ALT elevation (5%).[21] 16% of patients discontinued cabozantinib due to TRAEs, most commonly for PPES, fatigue, reduced appetite, diarrhea, and nausea.

In the study, grade 5 TRAEs were reported in 6 patients in the cabozantinib group, including liver failure, bronchoesophageal fistula, portal vein thrombosis, upper GI hemorrhage, pulmonary embolism, and hepatorenal syndrome.[21]

1.4.2 Pembrolizumab drug profile

Please refer to the Investigator's Brochure for complete information on pembrolizumab.

1.4.2.1 Preclinical and clinical trial data

Pembrolizumab is a potent and highly selective humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has been in clinical development in multiple advanced malignancies and has an acceptable safety profile.

Keytruda™ (pembrolizumab) has been approved for advanced or metastatic melanoma, non-small cell lung cancer, head and neck squamous carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, MSI-H or dMMR solid tumors, PD-L1-expressing gastric or gastroesophageal cancer, PD-L1-expressing cervical cancer, primary mediastinal large B-cell lymphoma, and Merkel cell carcinoma. Moreover, it was approved on November 9, 2018 for patients with advanced HCC previously treated withsorafenib.

Please refer to the Investigator's Brochure and the US Prescribing Information on pembrolizumab for more information.

1.4.2.2 Safety of pembrolizumab in HCC patients

The KEYNOTE-224 trial was a Phase 2 non-randomized trial of pembrolizumab in patients with HCC and Child-Pugh class A hepatic function (n=104).[35] Pembrolizumab was safe and tolerable in this population. TRAEs occurred in 73% of patients, with grade 3-4 TRAEs in 25% and SAEs in 15% of patients. The most common TRAES in >=10% of patients were: fatigue (21%), AST elevation (14%), pruritis (12%), diarrhea (11%), and rash (10%). The most common grade 3-4 TRAEs were: AST elevation (7%), ALT elevation (4%), and fatigue (4%). 17% of patients had a dose interruption due to a TRAE, most commonly AST elevation (4%), ALT elevation (3%), hypothyroidism (2%), and rash (2%). Five out of 104 patients discontinued pembrolizumab due to a TRAE, including adrenal insufficiency, increased AST, increased ALT, increased bilirubin, and cholestatic jaundice. One death due to ulcerative esophagitis was thought to be possibly related to pembrolizumab. Immune-related AEs (irAEs) were reported in 15% of the study population, most commonly hypothyroidism (8%) and adrenal insufficiency (3%). The rate of immune-mediated hepatitis was 3%; no flares or recurrence of HBV or HCV were observed. Four out of 104 patients had a grade 3 irAE: adrenal insufficiency (n=2), skin toxicity (n=1), and Type 1 diabetes mellitus (n=1).

In the Phase 3 trial KEYNOTE-240 of pembrolizumab vs. best supportive care, TRAEs occurred in 61% and 49% of patients, respectively. In the pembrolizumab arm, the rate of grade 3-4 TRAEs was 19%, while 7.2% of patients had a grade 3 immune-mediated AE, leading to treatment discontinuation in 7%. The most common TRAEs were: pruritis (13%), fatigue (10%), AST elevation (9%), diarrhea (8%), and rash (8%). The most common grade 3-4 TRAEs were: AST (5%) and ALT (4%) elevations. Hypo- (5%) and hyperthyroidism (3%) were the most common immune-mediated AEs, mostly grade 1-2, followed by severe skin reaction (3%), pneumonitis (2%), hepatitis (2%).[36]

Please refer to the pembrolizumab Investigator's Brochure for the complete drug safety and toxicity profile in other tumor types.

1.5 Rationale for dose selection

1.5.1 Rationale for cabozantinib dose selection

Cabozantinib will be initiated at 40 mg orally once daily continuously. In the CELESTIAL trial, 62% of

patients treated with cabozantinib 60 mg required a dose reduction due to toxicities, and the median average daily dose was 35.8 mg.[21] Ongoing trials of nivolumab and cabozantinib for triple negative breast cancer and renal cell carcinoma currently use a starting dose of 40 mg.[54-56] In fact, the 40 mg dose is recommended by Exelixis in trials of combination therapy with immune checkpointinhibitors.

1.5.2 Rationale for pembrolizumab dose selection

The planned fixed dose of pembrolizumab for this study in combination with cabozantinib is 200 mg IV every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type.

As outlined below, this dose is justified by:

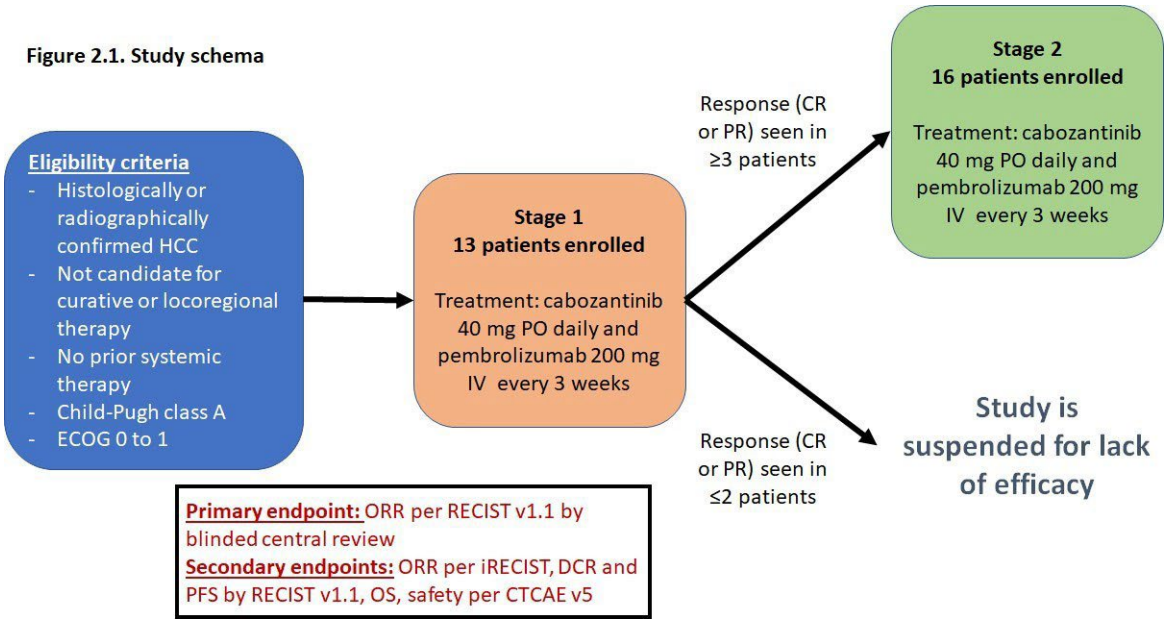
- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis)at 200 mg Q3W

Recently, the efficacy and safety of pembrolizumab 200 mg IV q3w in combination with the multikinase inhibitor lenvatinib has been evaluated in an investigational multicenter, multi-indication, open-label Phase 1b/1 clinical study[38] and a Phase 3 study is ongoing.

2.0 TRIAL DESIGN

This is a non-randomized Phase 2 trial using the Simon's optimal two-stage design. In the first stage, 13 eligible patients will enroll. If there are 2 or fewer patients with response (CR or PR), the study will be suspended for lack of sufficient efficacy. Otherwise, 16 additional patients will be accrued for a total of 29 patients. An accrual period of 24 months and follow-up period of 12 months are anticipated. More than 29 patients may be screened and/or enrolled depending on screen fails and dropouts before starting treatment.

Figure 2.1. Study schema



3.0 STUDY OBJECTIVES

3.1 Primary objectives

- To determine the objective response rate (ORR) of the combination of cabozantinib and pembrolizumab in the first-line treatment of advanced HCC based on RECISTv1.1.

3.2 Secondary objectives

- To assess the disease control rate (DCR) by RECIST v1.1, ORR and DCR by iRECIST, progression-free survival (PFS) by RECIST v1.1, and overall survival(OS).
- To assess the safety of the combination treatment with cabozantinib and pembrolizumab basedon NCI CTCAE v5.

3.3 Exploratory objectives

- To explore the predictive biomarkers for cabozantinib and pembrolizumab in HCC using archival tissue or pre-treatment fresh tumor biopsy (if available) and pre-treatment peripheralblood.

4.0 STUDY ENDPOINTS

4.1 Primary endpoint

- Objective response (complete or partial response) per RECIST v1.1 (by blinded central review).

4.2 Secondary endpoints

- Objective response (complete or partial response) per iRECIST (blinded central review).
- Disease control (complete + partial response + stable disease) per RECIST v1.1 and iRECIST.
- Progression-free survival (PFS) is defined as time from study registration to radiographic progression per RECIST v1.1 (blinded central assessment), clinical progression, or death of any cause.
- Overall survival (OS) is defined as time from study registration to death of any cause.
- Safety will be evaluated by assessing AEs according to NCI CTCAE v5.

4.3 Exploratory endpoints

Exploratory biomarkers will be assessed using archival tumor tissue or pre-treatment fresh tumor biopsy (if available) and peripheral blood and correlated with tumor response. Tumor tissue will be assessed by multiplex immunohistochemistry (IHC) assay for intratumoral immune cell subsets and distribution, RNA sequencing (NanoString) for immune gene expression, and T cell receptor (TCR) clonality. The expression levels of biomarkers including c-MET, PD-L1 and PD-L2 in tumor cells and cells of the tumor microenvironment will also be assessed by IHC. Blood-based biomarkers will be explored, including circulating T cell subsets and cytokines.

5.0 SUBJECT SELECTION

To be eligible for the study, the subject must meet all of the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion criteria

1. At least 18 years of age.
2. Must have a histologically confirmed diagnosis of HCC or a non-invasive diagnosis of HCC as per the American Association for the Study of Liver Diseases (AASLD) criteria.
   c. If available, archival tissue must be submitted.
   d. Mixed HCC-cholangiocarcinoma is not allowed.
3. Patient has BCLC stage C disease, or BCLC stage B disease that is not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to curative treatment.
   a. Previous locoregional therapy is allowed (e.g. surgical resection, external beam radiation, catheter-based therapy), and patients must have evidence of disease progression from locoregional therapy.
4. Must have measurable disease by RECIST v1.1.
   a. Lesions that were previously radiated or ablated cannot be target lesions unless there was subsequent radiographic progression at those sites.

5. No prior systemic therapy for HCC. Prior chemotherapy given locally into the liver (e.g. TACE) is allowed.
6. Must have Child-Pugh class A hepatic function within 7 days prior to first dose of study intervention (Appendix 6).
7. ECOG performance status 0-1 (Appendix 5).
8. Life expectancy of at least 12 weeks.
9. Recovery to baseline or ≤ Grade 1 toxicities (CTCAE v5) related to any prior treatments, unless adverse events (AEs) are clinically nonsignificant and/or stable on supportive therapy.
10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 without granulocyte colony-stimulating factor support.
    b. Platelets ≥ 60,000/mm^3 without transfusion within 14 days.
    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion or EPO dependency within 14 days.
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN).
    e. Total bilirubin ≤ 2 mg/dL OR direct bilirubin ≤ ULN for participants with total bilirubin levels >2 mg/dL.
    f. Serum albumin ≥ 2.8 g/dl (≥ 28 g/L) without albumin infusion.
    g. Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≤ 1.5 × ULN.
    h. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation (Appendix 7).
    i. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) or 24h urine protein ≤1g.
    j. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization or fasting serum glucose ≤ 160 mg/dL.
11. Patients with positive hepatitis B surface antigen (HBsAg) and/or HBV viral load >100 IU/mL at the time of enrollment are eligible to enroll on study if they meet the following criteria:
    a. Anti-HBV therapy as per institutional practice must be given at least 4 weeks and HBV viral load must be <100 IU/mL prior to initiating study treatment. Patients on active HBV therapy with viral loads <100 IU/mL should remain on the same therapy throughout study treatment.
    b. Note: Patients with positive anti-hepatitis B core antibody (HBcAb), negative HBsAg, and negative or positive anti-hepatitis B surface antibody, and who have an HBV viral load <100 IU/mL do not require anti-viral prophylaxis.
12. Patients with past or ongoing hepatitis C infection (HCV) are eligible to enroll on study, with or without prior anti-viral treatment, as long as the other eligibility criteria are met. Treated patients must have completed their anti-viral treatment at least 1 month prior to initiating study treatment.
13. Sexually active fertile subjects and their partners must agree to use effective methods of contraception (see Appendix 8) during the course of the study and for at least 4 months after the last dose cabozantinib. They must also refrain from donating sperm during this time period.
14. Female subjects of childbearing potential must not be pregnant at screening and not breastfeeding. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e. females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy).
    a. Women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.
15. Capable of understanding and complying with the protocol requirements and must provide written informed consent/assent for the study.

5.2 Exclusion criteria

1. Prior treatment with any systemic therapy for HCC, including anti-VEGF therapy or any systemic investigational agent.
   a. If the patient previously received systemic treatment for reasons other than HCC: small molecule kinase inhibitors are not allowed within 2 weeks and cytotoxic/biologic agents are not allowed within 4 weeks of study treatment.
2. Prior exposure to immune checkpoint inhibitors or other immunotherapeutic agents.
3. Currently participating in or has participated in a study of an investigational agent or device within 4 weeks prior to the first dose of study treatment.
4. Major surgery within 6 weeks or minor surgery (e.g. dental extraction) within 10 days prior to first dose of study treatment.
   a. Complete wound healing from major surgery must have occurred at least 1 month before first dose and from minor surgery (e.g. simple excision, tooth extraction) at least 7 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
5. Local liver-directed therapy within 4 weeks of initiating study treatment.
6. Palliative radiation for the purpose of symptomatic relief to non-liver and non-CNS disease within 2 weeks of starting treatment. Other radiation treatments within 4 weeks of starting treatment.
   a. Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and have not had radiation pneumonitis.
7. Prior liver or other allogenic tissue/organ transplantation.
8. History of primary immunodeficiency.
9. Active autoimmune or inflammatory disease that has required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). This includes, but is not limited to, inflammatory bowel disease, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, Graves' disease, etc.
   a. The following autoimmune conditions are allowed: vitiligo or alopecia; hypothyroidism on stable hormone replacement therapy; psoriasis/eczema not requiring systemic treatment.
   b. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
10. Chronic use of systemic steroid (in dosing exceeding 10 mg daily of prednisone equivalent) or immunosuppressive therapy or use within 14 days prior to enrollment.
    a. The following treatments are allowed: intranasal, inhaled, topical or local steroid injections; systemic corticosteroids at physiologic doses equivalent to no more than prednisone 10 mg/day; steroids as premedication for contrast dye allergy.
11. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. History of hepatic encephalopathy or treatment to prevent or control encephalopathy within the past 12 months. Subjects on lactulose and/or rifaximin to control hepatic encephalopathy are not allowed.
13. Esophageal or gastric variceal bleeding within the past 6 months. All subjects will be screened for esophageal varices unless performed in the last 6 months before study treatment. If varices are present, they should be treated according to institutional standards before starting study treatment.

14. Uncontrolled ascites, clinically significant or symptomatic ascites requiring paracenteses or increasing doses of diuretics within the past 3 months.
    a. Patients who are on stable diuretic doses for at least 3 months are eligible if they meet other eligibility criteria.
    b. Asymptomatic ascites detected on imaging are allowed.
15. Has known history or any evidence of CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are asymptomatic and radiologically stable (i.e. without progression for at least 4 weeks by repeat imaging (which must be performed during study screening), clinically stable, and without the need steroids for at least 4 weeks prior to first dose of study treatment).
16. Concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g. clopidogrel). Allowed anticoagulants are thefollowing:
    a. Low-dose aspirin for cardioprotection (per local applicable guidelines) ispermitted.
    b. Low molecular weight heparin (LMWH) is permitted.
    c. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 4 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
17. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias with risk of hemodynamic instability within 12 months before the first dose of study treatment.
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolicor > 95 mm Hg diastolic despite optimal antihypertensive treatment, and/or change in antihypertensive medications within 1 week before starting treatment. Note: eligibility of a subject receiving 4 or more antihypertensive medications prior to study entry will require approval from the PI.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or arterial thromboembolic within 12 months before the firstdose.
        iv. Asymptomatic venous thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism) is allowed if the patient has been stable on anticoagulation with LMWH for at least 4 weeks.
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g. Crohn's disease), GI malabsorption, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outletobstruction.
        ii. 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.
    c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, other history of significant bleeding (e.g. pulmonary hemorrhage) within 12 weeks before first dose, or known thrombotic disorder.
    d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial diseasemanifestation.

~~f.~~e. Lesions invading any major blood vessels, including inferior vena cava or cardiac involvement of HCC based on imaging.
Note: Main and branch portal vein and hepatic vein invasion is allowed.

~~g.~~f. Ongoing active infection requiring antibiotics. Antibiotics must be completed at least7 days before initiating study treatment.

~~h.~~g. Known active tuberculosis.

~~i.~~h. Serious non-healing wound, ulcer, or bone fracture.

18. Patients with proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 hours will be ineligible.
19. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (EKG) within 28 days before first dose of study treatment.
    a. Note: If a single EKG shows a QTcF with an absolute value > 500 ms, two additional EKGs at intervals of approximately 3 min must be performed within 30 min after the initial EKG, and the average of these three consecutive results for QTcF will be used to determineeligibility.
20. Inability to swallow tablets or any other condition that might interfere with oral absorption of medications.
21. Previously identified allergy or hypersensitivity to study drugs and/or any of theirexcipients.
22. Ongoing secondary malignancy that is progressing and/or has required active treatment within the past year. Adjuvant treatment for resected breast cancer is allowed.
    a. Subjects with basal cell carcinoma of the skin, squamous cell carcinoma or the skin, prostate cancer, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are allowed.
23. Has a known history of HIV infection. Note: HIV testing is not mandated forscreening.
24. Co-infection with HBV (HBsAg (+) and /or detectable HBV DNA) and HCV (anti-HCV Ab (+)and detectable HCV RNA) at study entry.
25. Co-infection with HBV and HDV at study entry.
26. Live vaccine or live attenuated vaccine within 30 days prior to first dose of studytreatment. Administration of killed vaccines is allowed.
27. Pregnant or lactating females.
28. Known psychiatric illness, substance abuse disorder, or other condition that would interfere with the ability to comply with the requirements of the study.
29. Has history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

5.3 Re-screening

Patients who failed initial screening due to a reversible cause (e.g. biliary obstruction, infection) may have an opportunity to re-screen after discussion with the Study PI.

6.0 PRE-TREATMENT PROCEDURES

This study will be initiated only after the protocol, informed consent form, and any other required documents have been reviewed and approved by the responsible IRB according to applicable regulations. The same applies for the implementation of changes introduced by amendments to the protocol or consent form, except where such changes are necessary to prevent apparent immediate hazards to the research participant(s) or others.

Potential patients will be identified in the GI Oncology outpatient clinics at Fred Hutchinson Cancer Center (FHCC) and through referrals from outside physicians or the Liver Tumor Clinic at the University of Washington Medical Center (UWMC). Patients who are potentially eligible for this trial will undergo the informed consent process and be screened for eligibility utilizing the Eligibility Criteria (Section 5.0).

6.1 Informed consent

Prior to participation in the study, written informed consent and HIPAA authorization must be obtained by the investigator (or person designated by the investigator) from each subject in accordance with regulatory, legal, and institutional requirements. The protocol will be discussed thoroughly with the subject, and all known risks will be described. The procedures and alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the study explained. The subject will be informed of the planned use, level of confidentiality, and potential disclosure of study data.

Consent will be obtained using forms approved by the Institutional Review Board (IRB) of the FHCRC/UW Cancer Consortium, which will be kept in the medical record. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood. A summary of the consent discussion will be recorded in the patient's medical chart. A signed copy of the informed consent will be given to each subject.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

6.2 Screening

Written informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration.

6.3 Subject registration

Once screening procedures are completed and eligibility is confirmed, the study subject will be registered and entered into the Clinical Trial Management System (CTMS) at the Fred Hutchinson Cancer Center. All patients must be registered and be assigned a unique study number prior to starting protocol therapy. Treatment initiation must occur within 5 working days of registration.

If a patient is consented to the trial but is not registered or is withdrawn prior to initiation of protocol treatment, the reason for screen failure and/or withdrawal will be documented. However, no clinical trial data will be collected beyond the basic demographic data contained on the eligibility checklist. A registration log with dated entries for each patient registered will bekept.

7.0 TREATMENT PLAN

All enrolled patients will be treated with cabozantinib and pembrolizumab in 3-week treatment cycles.

7.1 Cabozantinib administration

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.

All patients will be given the Cabozantinib Drug Diary (Appendix 2) to record the date and time of each dose of cabozantinib taken.

7.2 Pembrolizumab administration

Pembrolizumab will be administered at 200 mg intravenously over 30 minutes on Day 1 of each 3-week cycle (+/- 2 days). Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, a window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes -5 min/+10 min). Pembrolizumab should be infused before cabozantinib when the study drugs are given on the same day. The Pharmacy Manual contains specific instructions for the preparation of pembrolizumab and administration of infusion solution.

Pembrolizumab may be administered up to 2 days before or after the scheduled day of dosing due to administrative reasons. Dosing interruptions/delays are permitted in the case of medical/surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, patient vacation, holidays) not related to pembrolizumab-induced toxicity. Patients should resume pembrolizumab therapy within 3 weeks of the scheduled interruption (for reasons other than toxicity), unless approved by the Study PI. The reason for interruption/delay should be documented in the patient's study record.

7.3 Duration of therapy

Patients will begin cabozantinib and pembrolizumab concurrently. Patients may continue study therapy until unequivocal disease progression, unacceptable drug-related toxicity, or subject withdrawal. If one drug needs to be permanently discontinued due to toxicity, the other agent may be continued. Interval dosing interruption/delay of either or both agents is allowed for AEs (see Section 9.0).

Treatment beyond progression with cabozantinib and/or pembrolizumab (depending on patient tolerance) will be allowed based on meeting pre-specified criteria and after discussion with the study PI (see Section 12.1).

Patients may be treated up to a maximum of two years from the time of treatment initiation.

7.4 Treatment compliance

Patients will complete the Cabozantinib Drug Diary (Appendix 2) that helps with tracking of drug doses taken and confirming treatment compliance. Patient compliance with cabozantinib will be assessed at each visit. Compliance will also be confirmed by counting returned capsules.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she misses 7 or more consecutive days of cabozantinib, or more than 25% cumulative days of cabozantinib during the study for reasons other than toxicity, or if the patient takes more than the prescribed amount of medication. Cabozantinib dose suspensions or delays due to toxicity do not count in compliance assessment.

8.0 CONCOMITANT MEDICATIONS AND THERAPIES

8.1. Allowed therapy

During study participation, symptomatic or supportive treatment of tumor-associated symptoms (e.g. pain, nausea) and side effects of treatment is encouraged if appropriate as per the treating investigator.

Specifically, the following concomitant therapies are permitted, if clinically indicated:

- Antiemetics and antidiarrheal (for non-immune diarrhea) medications.
- Opioid analgesics.
- Granulocyte colony-stimulating factors (G-CSF) used as per clinical guidelines (e.g. ASCO or ESMO guidelines).
- Bisphosphonates can be used for bone metastases or hypercalcemia if the benefit outweighs the risk per the investigator's discretion.
    - Note: Osteonecrosis of the jaw has been reported with the use of bisphosphonates as well as with cabozantinib. Patients must be informed of this risk and be monitored frequently for

potentially overlapping toxicities. They should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Oral examinations are recommended prior to starting bisphosphonates. See Section 9.3.8.

- Transfusions and hormone replacement as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
    - *Therapeutic doses of LMWH* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 4 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.
    - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (e.g. for the treatment of DVT), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, see Section 9.3.4.
    - Standard clinical management of 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).
    - For restrictions on oral anticoagulants, see Section 8.4.
- Premedication is allowed for pembrolizumab-related infusion reactions (Section 9.5.6).

Patients cannot receive systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator. Exception: steroids may be used for premedication prior to imaging.

Potential drug interactions with cabozantinib are summarized in Section 1.4.3.

8.2 Recording concomitant therapy

Concomitant medications administered within 28 days before the first dose of study treatment and during the treatment phase until the study discontinuation visit should be recorded, as well as medications administered for SAEs occurring after 30 days after the last dose of trial treatment, as defined in Section 16.1.

All premedications, supportive medications, and other concomitant therapy (including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids) that are taken between study consent and the end-of-study visit after treatment discontinuation should be recorded in the case report form (CRF), with the start and end of treatment dates, total daily dose, dosage unit, and the reason for use. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

8.3 Palliative radiation

Limited data are available with cabozantinb and pembrolizumab and radiotherapy. Thus, palliative radiation should only be undertaken if medically necessary and indicated.

If radiation is undertaken, only palliative radiation to symptomatic bone metastases and limited to non-target lesions is allowed. Moreover, study treatment with both cabozantinib and pembrolizumab will be held at least 1 week before and resumed at least 1 week after radiation with complete recovery from acute toxicities of radiotherapy. The start and end dates of radiation, as well as the suspension and resumption dates of cabozantinib and pembrolizumab must be recorded in the CRF.

8.4 Prohibited or restricted therapy

The following therapies are prohibited from the time of screening until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulants (e.g. warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).
- Any non-protocol systemic anticancer treatment (e.g. chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).
- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery on target lesions used for response monitoring by RECIST v1.1.
    - Note: radiation therapy to a symptomatic solitary lesion or to the brain that is not a target lesion may be allowed at the investigator's discretion.
- Anti-HCV therapy.
- Live vaccines or live attenuated within 30 days prior to the first dose of study treatment and while participating in the study. Administration of killed vaccines is allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

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

- Erythropoietic stimulating agents (e.g. epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTcinterval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (Appendix 4)

may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended if possible.
- 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 (Appendix 4) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended if possible.

Additional information on potential drug interactions with cabozantinib is provided in Section 1.4.3.

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

The risks of solid organ transplantation following treatment with PD-1 inhibitor therapy have not been extensively studied. The time frame for safe or appropriate liver transplantation after the last dose of pembrolizumab is unknown. Therefore, it is recommended not to perform liver transplantation within at least 120 days (5 half-lives) of stopping pembrolizumab. The risks and benefits of transplant should be discussed with the participant by the treating investigator.

9.0 TOXICITIES AND DOSING MODIFICATIONS

9.1 Assessment of adverse events

The patient's pre-existing conditions will be recorded, including signs and symptoms of the disease. Subjects will be monitored for AEs from the time of informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib or pembrolizumab treatment, whichever occurs last). Subjects will be instructed to notify the investigator immediately at the onset of any AE experienced. Moreover, AEs will be assessed at scheduled study visits or non-study clinic visits. In addition, any SAE attributed to treatment occurring after the last follow-up visit will also be recorded.

All AEs and changes in pre-existing conditions will be documented, whether related or unrelated to study treatment. Seriousness, severity grade, and relationship to study treatment or protocol procedure will be determined by the investigator and reported on the CRF. The NCI CTCAE v5 will be used to grade AEs. For AEs not listed in the CTCAE v5, the investigator will be responsible for selecting the appropriate system organ and severity grade based on their clinical judgement. SAEs that occur after signing the consent form but prior to receiving study treatment will not be reported as serious unless the event was caused by a protocol procedure.

See Section 16.0 for definitions and guidelines on monitoring and reporting of AEs and SAEs.

9.2 General guidelines about toxicity assessment and management in combination therapy

Both non-immune and immune-related toxicities may occur on study. Any AE that occurs on study will be assessed for grade and attribution to either cabozantinib, pembrolizumab, or both agents.

Cabozantinib and pembrolizumab have class-specific safety profiles based on their mechanisms of action but may also cause overlapping AEs. Examples of VEGFR TKI-associated AEs caused by cabozantinib are hypertension and hand-foot syndrome. Examples of immune-related AEs caused by pembrolizumab are pneumonitis and endocrinopathies. Examples of overlapping AEs are diarrhea and ALT or AST elevations. To distinguish the toxicities of these two agents, the known toxicity profiles and typical timeline of toxicities associated with both study drugs should be taken into account.[57] For instance, in the CELESTIAl trial, the median onset of diarrhea among patients who received cabozantinib was 4.1 weeks.[21] Immune-related AEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment, and may affect more than one organ system simultaneously.

Therefore, if an AE is believed to be possibly related to or exacerbated by cabozantinib only, then it must be managed accordingly and cabozantinib may need to be interrupted and/or dose-adjusted. In this setting, pembrolizumab may be continued if the patient can tolerate it as per discretion of the investigator. However, it is recommended to hold pembrolizumab as well in the setting of severe (grade 3 or higher) AEs related to cabozantinib alone.

In contrast, if an AE is believed to be possibly related to or exacerbated by pembrolizumab,, then both agents should be interrupted according to the guidelines below, even if the AE is not attributed to cabozantinib.

For immune-related AEs (irAEs), early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study 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, pembrolizumab may be held or permanently discontinued and steroids may be administered.
Guidance on dose modification of cabozantinib and pembrolizumab in the setting of specific AEs is provided in Sections 9.3 and 9.5, but management may differ from this guidance based on the clinical judgement of the investigator.

If one agent needs to be discontinued indefinitely due to toxicity, the other agent may be continued if the patient can tolerate it as per discretion of the investigator.

All dose interruptions and adjustments must be recorded clearly and accurately in the CRF, including dates of stopping and resuming drug(s), doses, and reasons for changes. In the event of a treatment pause, subsequent visits/cycles should not be delayed.

9.3 Information on cabozantinib toxicity

AEs may occur within the first few weeks after starting cabozantinib (steady state reached at approximately 2 weeks). Cabozantinib-related AEs that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.

AEs should be managed with supportive care at the earliest signs of toxicity. In all subjects, dose delays and reductions of cabozantinib to manage toxicity are allowed under the guidelines below. In general, grade 3 cabozantinib-related AEs require dose interruption until AEs recover to grade 1, at which point treatment may be resumed at the next lower dose. Moreover, dose reductions are recommended for

grade 2 events that, if persistent, could become serious and/or intolerable. **If cabozantinib is delayed by more than 4 weeks, it must be discontinued**, unless there is reason to believe that the patient will benefit from resuming cabozantinib. In this case, resuming cabozantinib at dose reduction must be discussed with the PI.

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

If an AE is believed to be probably/definitely related to cabozantinib, and not related to pembrolizumab, then pembrolizumab may be continued even if cabozantinib needs to be interrupted or discontinued, as long as pembrolizumab is not expected to delay recovery or worsen the AE.

9.3.1 Gastrointestinal disorders

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

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool, or an increased frequency of bowel movements. **Please see Section 9.5.2 for evaluation and management of diarrhea and specific dosing instructions for both cabozantinib and pembrolizumab.**

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Patients should be monitored for dehydration and electrolyte abnormalities, and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (see Section8.0).

9.3.2 Non-gastrointestinal fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

9.3.3 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding with clinical and laboratory assessments 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 hemorrhageoccur.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood). For other clinically significant bleeding events, cabozantinib may be held and resumed after the bleeding resolves.

9.3.4 Thromboembolic events

Cancer patients are at increased risk of venous thromboembolic events. 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 their study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with DVT or pulmonary embolism if it is determined that the event is uncomplicated, the patient is relatively asymptomatic, and anticoagulation does not place them at a significant risk per discretion of the investigator.

LMWHs are the preferred management for thrombotic events. Oral anticoagulants (e.g. warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

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

9.3.5 Hypertension

BP should be monitored in a sitting position in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by an experienced health care provider and must be confirmed with a second measurement at least 5 minutes following the firstmeasurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

The management of hypertension related to cabozantinib is outlined in Table 9.3.5.1.

Table 9.3.5.1. Management of hypertension associated with cabozantinib	
Criteria for dose modification	**Management and cabozantinib 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 antihypertensive medications and/or increase the 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 and resume once BP <150 mm Hg systolic or <100 mm Hg diastolic and symptoms resolve.
≥ 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 anti-hypertensive medications and/or increase the dose of existing medications. • 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 and resumed at dose reduction (if not already done) when BP <150 mm Hg systolic or <100 mm Hg diastolic. • Cabozantinib treatment should be interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable, if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic. • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic.
Hypertensive emergency[c]	• Discontinue cabozantinib treatment.

BP, blood pressure.

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

[b] Permitted dose levels are defined in Section 9.4.

[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).

9.3.6 Stomatitis and mucositis

Preventive measures before study treatment are recommended, 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 gentle 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.

Cabozantinib should be interrupted for drug-related grade 3 stomatitis and mucositis until symptoms improve to grade 1, followed by resumption of drug at the next lower dose.

9.3.7 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. **Recommendations for treatment of PPES and dose modification of cabozantinib are summarized in Table 9.3.7.1.**

For other skin toxicities, including possible immune-mediated skin rash, please see Section 9.5.4.

Table 9.3.7.1. Management of hand-foot syndrome (PPES) associated with cabozantinib

Grade per CTCAE v5	Management and cabozantinib modification
Grade 1: Minimal skin changes or dermatitis (e.g. erythema, edema, or hyperkeratosis without pain)	Cabozantinib treatment should be continued at the current dose. Start urea 20% cream twice daily and consider mild-moderate potency steroid topical.. If PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2: Skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with	Cabozantinib treatment may be continued at same dose, dose-reduced, and/or interrupted at the discretion of the treating investigator depending on the degree of symptoms. Continue urea 20% cream twice daily AND add a high potency steroid topical, and add analgesics for pain control if needed. If PPES worsens or affects self-care, proceed to the intervention guidelines for

pain; limiting instrumental ADL	Grade 3.
Grade 3: Severe skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL	Interrupt cabozantinib treatment until severity decreases to Grade 1. Continue treatment of skin reaction with high potency steroid cream and analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 4 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.
[1]Permitted dose levels are defined in Section 9.4.

9.3.8 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.

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

Dental surgery or 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.

Withhold cabozantinib for development of ONJ until complete resolution.

9.3.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR once every 6 weeks (every 2 cycles) on treatment, and more frequently if abnormal. **Table 9.3.9.1 provides treatment guidelines for proteinuria related to cabozantinib.**

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

Table 9.3.9.1. Management of proteinuria associated with cabozantinib	
Severity of proteinuria (UPCR)	**Management and cabozantinib modification**
≤ 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. • After dose reduction or interruption, repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to once monthly. (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 once monthly 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 once monthly or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib.

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

9.3.10 Nervous system disorders

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

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

9.3.11 Hepatocellular toxicity

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver

conditions (e.g. liver cirrhosis, liver metastases, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer-related causes. Specifically, pembrolizumab is a potential cause of immune-mediated hepatitis and reactivation or flare of HBV or HCV in affected patients is a possibility. **Please see Section 9.5.3 for evaluation and management of liver toxicity and specific dosing instructions for both cabozantinib and pembrolizumab.**

9.3.12 Infections and infestations

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted if there are open wounds until adequate healing has taken place. For minor or mildly symptomatic infections (e.g. urinary tract infection, cellulitis), cabozantinib may be continued at the discretion of the investigator if the drug is believed to be unrelated and is not expected to worsen the infection.

9.3.13 Blood and lymphatic system disorders

Hematological toxicities (e.g. neutropenia, thrombocytopenia) have been observed after administration of cabozantinib. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

See Section 9.5.1 for guidance on dose modification of cabozantinib for hematologic toxicities. The use of colony-stimulating growth factors may be considered for significant neutropenia (e.g. grade 3 or higher) believed to be related to cabozantinib. 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, with interruption of study treatment until resolution.

Supportive care for thrombocytopenia or anemia, such as transfusions, may be considered according to institutional guidelines. However, if there is a recurrent need for transfusions or grade 3 events, dose reduction of cabozantinib to the next lower dose is recommended.

9.3.14 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.

For clinically significant fatigue (e.g. grade 3) related to or exacerbated by cabozantinib, dose interruption and/or dose reduction is recommended.

9.3.15 Weight loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy may be considered for appetite enhancement when not prohibited if there is minimal drug interaction with cabozantinib (see Section 8.4).

For clinically significant weight loss or anorexia (e.g. grade 3) related to or exacerbated by cabozantinib, dose interruption and/or dose reduction is recommended.

9.3.16 QTc prolongation

The effect of orally administered cabozantinib 140 mg once daily on QTc interval was evaluated in a placebo-controlled study in subjects with medullary thyroid cancer. A mean increase in QTcF of 10-15 ms was observed at 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 CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

An EKG should be obtained every 2 cycles on treatment. At any time on study, if there is an increase in QTcF to an absolute value > 500 ms, two additional EKGs must be performed with intervals not less than 5 min apart within 30 min after the initial EKG.

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

- Interrupt cabozantinib treatment.
- Hospitalize symptomatic subjects (e.g. palpitations, dizziness, syncope, orthostatic hypotension, ventricular arrhythmia on EKG) 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 for concomitant medications that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org).

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted at a reduced dose level if all of the following conditions are met:

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

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

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

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

9.3.17 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 at least every 3 weeks while receiving cabozantinib. More frequent monitoring may be required. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

9.3.18 Angioedema

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to effects on airway. If life-threatening angioedema is probably or definitely related to cabozantinib, the drug must be discontinued.

9.3.19 Endocrine disorders

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib monotherapy treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance.

TSH elevation may also be related to immune-mediated endocrinopathy caused by pembrolizumab, which occurs in 8% and 5% of patients in the KEYNOTE-224 and KEYNOTE-240 trials, respectively (mostly grade 1-2).[35,36] TSH and free T4 and T3 should be checked at least every 6 weeks (every 2 cycles) on study.

Regardless of whether it is related to cabozantinib and/or pembrolizumab, clinically symptomatic hypothyroidism should be treated with thyroxine replacement as per accepted clinical practice guidelines. **See Section 9.5.5 for treatment guidelines for suspected immune-mediated endocrine AEs.**

9.4 Dose levels of cabozantinib

Cabozantinib must be started at 40 mg orally once daily and reduced to 20 mg orally once daily (minimum dose) for toxicity. Cabozantinib must be discontinued permanently if the minimal dose is not tolerated. Re-escalation to 40 mg once daily is not recommended, but may be allowed if there is a reason to believe that the patient will tolerate this dose after discussion with the PI.

Table 9.4.1. Dose levels for cabozantinib

Dose Adjustment Level	Oral Dose	Frequency
0 (starting dose)	40 mg	Once daily
-1	20 mg	Once daily
-2	Discontinue	

9.5 Guidance on dose modification of cabozantinib and pembrolizumab for non-immune and immune toxicities

Both non-immune and immune-mediated toxicities may occur on study.

The sections below provide guidance on dose modifications for TRAEs, in addition to management recommendations for cabozantinib-specific toxicities discussed in Section 9.3. However, management

may differ from this guidance based on the clinical judgement of the investigator. In all patients, supportive care should be initiated to manage the AEs in addition to dose modification of study drugs.

For potential irAEs, please refer to the ASCO Clinical Practice Guidelines for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy.[58]

If dose is interrupted for TRAEs, cabozantinib must be resumed within 4 weeks of last dose, and pembrolizumab must be resumed within 12 weeks of last dose. Resuming drugs beyond these time points must be discussed with the Study PI.

9.5.1 Non-immune toxicities

Table 9.5.1.1 below provides guidance for dose modification for non-immune toxicities in general. Pembrolizumab should be held if the AE is clinically severe and/or if pembrolizumab might delay recovery or worsen the AE.

Table 9.5.1.1. General guidance on dose modification for non-immune toxicities

Grade per CTCAE v5	Cabozantinib modification	Pembrolizumab modification
Hematologic TRAEs		
Grade 1 and 2	• No modification.	• No modification.
Grade 3 or 4 anemia, neutropenia, thrombocytopenia [1]	• Hold drug until recovery to grade 1, then restart at same dose level OR at reduced dose level (at the discretion of the investigator). • 1st and 2nd recurrence: hold drug until recovery to grade 1, then restart at reduced dose level (if not already reduced) or discontinue drug (if previously reduced dose).	• No modification. Consider holding drug if no improvement after holding cabozantinib.
Non-hematologic TRAEs		
Grade 1 or 2	• No modification (may be held for significantly symptomatic grade 2 toxicity). Supportive care as indicated.	• No modification.
Grade 3	• Hold drug until recovery to grade 1. If supportive care can be used and optimized to control symptoms, then restart at the same dose level. If grade 3 toxicity occurred on maximal supportive care then restart at reduced dose level.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.

	• 1st and 2nd recurrence despite optimal supportive care: hold drug until recovery to grade 1, then restart at reduced dose level (if not already reduced) or discontinue drug (if previously reduced dose).	
Grade 4	• Hold drug and provide supportive care until recovery to grade 1, then restart at reduced dose level if the patient is deriving clinical benefit as determined by the treating investigator. • 1st recurrence: discontinue drug.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.

TRAE, treatment-related adverse event.
[1]Supportive transfusions and use of G-CSF recommended as per institutional guidelines.
Note: Continuation of study drugs in the setting of asymptomatic grade 3-4 elevations of amylase/lipase is permitted after discussion with the study PI.

9.5.2 Diarrhea

Diarrhea is a known toxicity of both cabozantinib and immune checkpoint inhibitors such as pembrolizumab. In the CELESTIAL trial of cabozantinib (starting dose of 60 mg daily) vs. placebo, 54% of patients treated with cabozantinib had diarrhea of any grade, and 10% had grade 3 diarrhea. The median time of onset of diarrhea was 4.1 weeks.[21] In the KEYNOTE-224 trial of pembrolizumab, 11% of patients experienced diarrhea (all grade 1-2, no grade 3 or 4), while the rate of immune-mediated colitis was 1%.[35] In the randomized KEYNOTE-240 trial, diarrhea occurred in 16% of patients on the pembrolizumab arm (1.2% grade 3-4).[36]

The combination of multikinase inhibitor and immune checkpoint inhibitor may potentially increase diarrhea. However, the rate of diarrhea was similar with the combination of lenvatinib and pembrolizumab as observed in the early Phase 1b trial (any grade, 43%; grade 3, 3%) compared to lenvatinib alone (any grade, 39%; grade 3, 4%).[10,38]

Enrolled patients should be closely monitored for diarrhea, and if present, attribution to cabozantinib or pembrolizumab or both must be carefully considered. Timing may guide attribution, as the onset of diarrhea related to cabozantinib tends to occur shortly after starting drug (e.g. within 2 weeks), while the median time to onset of immune-related colitis related to pembrolizumab was 3.5 months with a median duration of 1.4 months.

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. Examination of the perianal region should be performed for reported perianal symptoms in patients experiencing diarrhea during treatment with cabozantinib/pembrolizumab. Infections of the perianal region should be treated per local guidelines.

General management for diarrhea:

- Monitor patients for signs and symptoms of colitis (e.g. diarrhea, abdominal pain, bloody stools, fever) and bowel perforation.Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management (e.g. loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Some subjects may require treatment with more than one antidiarrheal agent, and the addition of diphenoxylate/atropine and/or tincture of opium can be considered. In addition, general supportive measures should be implemented, such as increasing oral hydration (+/- IV isotonic fluids), correcting electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals and alcohol. When diarrhea resolves to baseline bowel habits, gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval.
- For grade 1 and 2 diarrhea: supportive measures as above.
- For intolerable grade 2 diarrhea or grade 2 diarrhea >48 hours despite optimal supportive measures as above:
    - Obtain labs to rule out dehydration and electrolyte abnormalities.
    - Rule out infectious diarrhea (e.g. stool culture, C difficile toxin, enteric panel).
    - If diarrhea lasts > 7 days, consider imaging (e.g. CT abdomen/pelvis) and GI consult for colonoscopy for biopsy.
- If infectious source is ruled out and diarrhea is persistent > 7 days, suspect immune-mediated colitisFor severe and/or life-threatening diarrhea:
    - Admit to hospital for IV hydration and electrolyte replacements.
    - Rule out infectious diarrhea (e.g. stool culture, C difficile toxin, enteric panel).
    - Obtain imaging (e.g. CT abdomen/pelvis) and GI consult for colonoscopy for biopsy.
    -
- See Table 9.5.2.1 for dosing of cabozantinib and pembrolizumab in the setting of non-immune diarrhea. For suspected immune-mediated colitis, also follow guidelines in Table 9.5.5.1.

Table 9.5.2.1. Guidance for diarrhea due to cabozantinib (non-immune)

Grade per CTCAE v5	Cabozantinib modification	Pembrolizumab modification
Grade 1 (< 4 stools/day over baseline)	• Continue at same dose.	• Continue at same dose.
Grade 2 (4-6 stools/day over baseline)	• Continue at same dose, or if intolerable grade 2 or grade 2 >48 hours despite optimal supportive measures and anti-diarrheals, hold drug until improvement to grade 1, then restart at same dose or at reduced dose (at the discretion of the investigator).	• Continue at same dose.

Grade 3 (7 or more stools/day over baseline)	• Hold drug until recovery to grade 1, then restart at same dose (if best supportive care was not previously used) or at reduced dose (if diarrhea is uncontrolled despite best supportive care). • 1st recurrence: hold drug until recovery to grade 1, then restart at reduced dose (if not already done) or discontinue drug (if dose previously reduced).	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.
Grade 4 (life-threatening)	• Hold drug until recovery to grade 1, then restart at reduced dose level if the patient is deriving clinical benefit as determined by the treating investigator. • 1st recurrence: discontinue drug.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.

9.5.3 Liver toxicity

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Moreover, temporary hepatic decompensation may occur especially in cirrhotic patients when exposed to a TKI.

It may be difficult to distinguish these lab abnormalities related to cabozantinib from immune-mediated hepatitis of pembrolizumab. Grade 3 immune-related hepatitis was observed in 3% of patients who received pembrolizumab in the KEYNOTE-224 trial,[35] while 7% of patients treated with pembrolizumab in

the KEYNOTE-240 trial experienced an immune-mediated hepatic event, although no HBV/HCV flares occurred.[36] Previous studies showed that immune-mediated hepatitis typically occurs during the first 6-12 weeks after initiating an immune checkpoint inhibitor.[59] Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares.

Hepatic events of clinical interest (HECI) are defined as:

- ALT:
  a: Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN
  b: Among subjects with baseline ALT ≥2×ULN: ALT >3× the baselinelevel
  c: ALT >500 U/L regardless of baseline level
- Total bilirubin:
  a: Total bilirubin >3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset clinically detectable ascites requiring intervention for >3 days
  - Hepatic ncephalopathy

General management for liver toxicity:

- In the setting of liver toxicity indicated by abnormal liver function tests (e.g. ALT, AST, ALP, total bilirubin, INR), monitor liver function **at least weekly** until recovery to baseline orstabilization.
- If there is grade 3 hepatic toxicity, it is recommended that both cabozantinib and pembrolizumab be interrupted and the patient be further evaluated. Consider causes of hepatitis and obtain appropriate workup, including disease progression, viral causes (HBV, HCV, EBV, CMV), drug- or alcohol-induced hepatitis, herbals, infection, biliary obstruction, etc.
- When an HECI occurs:
  - Hold study intervention and notify the Principal Investigator within 24 hours. All cases of retreatment after interruption of study intervention for HECI must be reported to the Principal Investigator and recorded in the database.
  - All participants should be considered for evaluation according to the directions below within 72 hours of onset:
    - Consider obtaining a consultation with a hepatologist.
    - Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus.
    - Assess for ingestion of drugs/supplements with hepatotoxic potential.
    - Assess for alcohol ingestion.
    - Assess for potential bacterial infection, biliary obstruction, or occultgastrointestinal bleeding.
    - Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, INR, and complete blood count with differential.
    - Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past).
    - HBV DNA, HBsAg, HBeAg, HBcAb (total and IgM), HBeAb, and HBsAb regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents).
    - Other laboratories or imaging studies as clinically indicated.
  - Consider liver biopsy if indicated.In the setting of HBV flare or change in HBV immunologicstatus:
    - Start antiviral therapy if appropriate

- Measure HBsAg and HBV DNA on **weekly** basis (if detected at the time of onset of HECI).
- Evaluate the following every 2-3 weeks if not detected at the time of onset of HECI
  - Anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of HECI)

- In the setting of HCV exacerbation in patients with positive HCV RNA, relapse of HCV in patients with previous antiviral treatment, or new HCV infection:
  - Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection.
  - Measure HCV RNA levels **every 2 weeks**.

- Please discuss risk benefit with Principal Investigator prior to starting HCV antiviral therapy.- If there are other causes of liver dysfunction, treat accordingly (e.g. biliary obstruction).

- The following table provides guidance on the dosing of cabozantinib and pembrolizumab in the setting of non-immune liver toxicity.
- If there is suspicion for possible pembrolizumab-mediated hepatitis, also follow the management outlined in Table 9.5.5.1:
- Cabozantinib may be held up to 28 days, and pembrolizumab may be held up to 12 weeks.
- Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation can indicate drug-induced liver injury (DILI) due to cabozantinib. Cabozantinib should be permanently discontinued in cases determined to be DILI according to Hy's Law review.
- Study treatment should be discontinued indefinitely if grade 3 hepatic dysfunction is not reversed despite dose interruption and treatment of potential causes including immune-mediated hepatitis.

Table 9.5.3.1. Guidance for liver toxicity due to cabozantinib (non-immune)

Grade per CTCAE v5	Cabozantinib modification[1]	Pembrolizumab modification[1]
ALT/AST > 5 x ULN if ALT/AST ≤ 2 x ULN at baseline OR ALT/AST 3-fold increase from D1 level BUT NOT EXCEEDING 8 X ULN if ALT/AST > 2 x ULN at baseline	• Hold drug until recovery to ≤ grade 2 ALT/AST elevation, then restart at reduced dose (consider resume at the same dose if other cause of liver toxicity found). • 1st recurrence: discontinue drug.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.
ALT or AST > 5 x ULN accompanied by total bilirubin ≥ 2 x ULN	• Hold drug until recovery to ≤ grade 1 ALT/AST and bilirubin elevation or pre-treatment baseline, then restart at reduced dose (consider resume at the same dose if other cause of liver toxicity found). • 1st recurrence: discontinue. • Note: A patient with Gilbert's syndrome should be managed according to observed elevation of ALT and/or AST if the observed bilirubin increase is below actual increased baseline bilirubin value.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.

Total bilirubin > 3.0 mg/dL irrespective of ALT/AST values	• Hold drug until recovery to ≤ grade 1 ALT/AST and bilirubin elevation, then restart at reduced dose (consider resume at the same dose if other cause of liver toxicity found). • 1st recurrence: discontinue.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.
	• Note: For a patient with Gilbert's syndrome, a continuation of cabozantinib might be considered at the discretion of the investigator if the observed bilirubin increase is below actual increased baseline bilirubin value.	
AST and/or ALT > 20 x ULN	• Discontinue drug.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.
Hepatic encephalopathy not reversible and manageable by therapy[2]	• Discontinue drug.[2]	• Discontinue drug.[2]
Child-Pugh score > 8 points[2]	• Discontinue drug.[2]	• Hold drug until Child-Pugh score < 8, then resume at drug.[2]
GI bleeding suggestive or portal hypertension (e.g. esophageal or gastric varices)	• Discontinue drug.	• Hold drug until bleeding has resolved and intervention completed if indicated (e.g. variceal banding) and patient is stable, then restart at the same dose as long as Child-Pugh score < 8 and ALT/AST/bilirubin elevations are < grade 3.

[1]Once dose reduced, cabozantinib dose cannot be increased. Cabozantinib may be held up to 28 days, and pembrolizumab may be held up to 12 weeks.

[2]Some TKIs may cause hepatic encephalopathy, which is reversible and manageable. Patients with transient deterioration to Child Pugh score > 8 due to an ongoing reversible process such as treatable infection or dehydration can be reassessed for up to 2 weeks; if liver function improves to Child Pugh 5-7, consider reintroduction of pembrolizumab monotherapy and subsequent reintroduction of cabozantinib 1-2 weeks later if Child Pugh is 5-6 after discussion with study PI.

9.5.4 Skin toxicity other than PPES

Dose modification of cabozantinib for hand-foot reaction (or PPES) is covered in Section 9.3.7. Oher skin rashes or abnormalities may occur due to cabozantinib.

General management of skin toxicities:

- Optimize supportive measures, including topical emollients, oral antihistamines, and medium- to high potency topical corticosteroids.
- For grade 2 and higher skin toxicity, monitor weekly for improvement.

- For grade 3 skin toxicity, consider referral to Dermatology.
- If a grade 3 rash does not improve within 7 days after stopping cabozantinib and pembrolizumab and providing optimal supportive measures, suspect immune-mediated skin toxicity.
- See Table 9.5.4.1 for dosing of cabozantinib and pembrolizumab for non-immune mediated skin toxicity. For immune-mediated skin toxicity, see Table 9.5.5.1.

Table 9.5.4.1. Guidance for non-immune skin and subcutaneous toxicity other than PPES (e.g. rash, erthymatous, follicular, macular, dermatitis, pruritis).

Grade per CTCAE v5	Cabozantinib modification	Pembrolizumab modification
Grade 1 or 2	• Continue at the same dose level.	• Continue at the same dose level.
Grade 3	• Hold drug until recovery to grade 2 or less, then restart at same dose or at reduced dose (at the discretion of the investigator). • 1st and 2nd recurrence: hold until recovery to grade 2 or less, then restart at reduced dose level (if not already reduced) or discontinue drug (if previously reduced dose).	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.
Grade 4 or Steven Johnson Syndrome of any grade	• Hold drug until recovery to grade 2 or less, then restart at reduced dose. • 1st recurrence: discontinue drug.	• Hold drug until recovery to grade 1 (or pretreatment baseline), then restart drug.

9.5.5 Immune-related toxicities

Immune-related AEs (irAEs) may occur after the first dose or several months later. Workup should be performed to rule out other causes. Most irAEs are reversible when the immune checkpoint inhibitor is stopped and steroids and supportive care are initiated. Depending on severity of irAEs, pembrolizumab may be resumed after recovery (after completion of steroid taper) or permanently discontinued.

The ASCO Clinical Practice Guidelines on the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy[58] provides a comprehensive overview of potential irAEs and management. Whenever possible, it is recommended that these guidelines befollowed.

General management for irAEs:

- Consider other causes and ensure adequate workup to rule out other etiology if applicable (e.g. infectious, drug-induced).
- Please see Table 9.5.5.1 for guidance on pembrolizumb dosing for specific irAEs. Whenever pembrolizumab is held for an irAE, cabozantinib should also be held. The latter can resumed when the irAE improves to grade 1 (even if pembrolizumab has not been restarted yet, e.g. during steroid taper).

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Table 9.5.5.1. Dose modification and toxicity management guidelines for other immune-related AEs..

General instructions:

1. Even if the AE is not related to cabozantinib, hold cabozantinib whenever pembrolizumab is held for an irAE.
2. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
3. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 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.
4. 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.
5. Cabozantinib may be restarted when the irAE improves to grade 1 at the discretion of the treating investigator. Cabozantinib should be restarted within 4 weeks of drug interruption (this may occur during steroid taper). If this must be restarted after 4 weeks after interruption for an irAE, please discuss with the Study PI.

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants 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		
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 participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants 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 (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroiddisorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroiddisorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids • Cabozantinib must be held until resolved to grade 0.	• Ensure adequate evaluationto confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluationto confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants 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).

9.5.6 Pembrolizumab-related infusion reaction

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 9.5.6.1. No dose modification is required for cabozantinib.

Table 9.5.6.1. 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 participant 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 participant 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 participant should be premedicated for the next scheduled dose. **Participants who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO/IV (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 participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant 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 CTCAEv5 at http://ctep.cancer.gov.		

9.6 Adverse events not related to study drugs

If an AE is unrelated to either cabozantinib or pembrolizumab (e.g. symptoms due to disease, concomitant medication/procedure, other illness), cabozantinib and pembrolizumab may be continued or held at the discretion of the investigator. In general, treatment may be continued if the AE is not treatment-related and not clinically significant, the patient is relatively asymptomatic and stable with good performance status, and if treatment will not delay recovery or worsen the AE. **If treatment is held for AEs unrelated to treatment, cabozantinib and pembrolizumab should be resumed at the same doses as previously within 4 weeks.**

10.0 STUDY CALENDAR

Table 10.1 summarizes the trial procedures to be conducted at various timepoints. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing not outlined in this table may be deemed necessary by the Principal Investigator for reasons related to participant safety.

Table 10.1. Baseline schedule of activities

1 cycle = 21 days	Baseline[17]	Cycle 1			Cycle 2+	Treatment discontinuation visit[19]	Follow-up[20]
		Day 1[18]	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	(+ 7 days)	(± 7 days)
TREATMENT							
Cabozantinib[1]		X	X	X	X		
Pembrolizumab[2]		X			X		
REQUIRED ASSESSMENTS							
Informed consent/HIPAA	X						
Inclusion/exclusion criteria[3]	X						
Medical and smoking history	X						
Disease and treatment history	X						
Vital signs, physical exam, ECOG status, weight[4]	X	X	X	X	X	X	
Height[5]	X						
AE and medications assessment[6]	X	X	X	X	X	X	
Cabozantinb Drug Diary Collection[7]		X			X	X	
CBC and differential[8]	X	X		X	X	X	
Serum chemistry[8]	X	X		X	X	X	
PT/INR, PTT	X	X			X	X	
Lactate dehydrogenase	X						
Hepatitis C antibody (+/- HCV RNA)[9]	X						
Hepatitis B core antibody[10]	X						
Hepatitis B surface antigen and/or HBV	X				X (q2C starting		

DNA[10]					at C3)		
TSH with reflex T4[11]	X				X (q2C starting at C3)		
Cortisol[11]	X				X (q2C starting at C3)		
Amylase[11]	X				X (q2C starting at C3)		
Lipase[11]	X				X (q2C starting at C3)		
Urinary protein to creatinine ratio[11]	X				X (q2C starting at C3)		
EKG[11]	X				X (q2C starting at C3)		
Esophagoduo-denoscopy (EGD) [12]	X						
Pregnancy test (WOCP only)	X						
Vital status, date of progression if applicable						X	X
DISEASE ASSESSMENT							
Alpha fetoprotein[13]	X				X (q3C starting at C4)	X	
Radiologic imaging by CT or MRI[14]	X				X (q3C starting at C4)	X	X
CORRELATIVE STUDIES							
Archival tumor tissue for research purposes if available. Otherwise, fresh biopsy is optional.[15]	X						
Blood collection[16]		X	X		X (C2D1 only)		

Footnotes

[1]Daily continuously starting at Cycle 1 Day 1. See Section 9.0 for dose modifications.

[2]Dosed on Day 1 of each 3-week cycle. See Section 9.0 for dose modifications.

[3]See Section 5.0 for inclusion and exclusion criteria.

[4]Vital signs include: blood pressure, pulse, respiratory rate, oxygen saturation, temperature. Blood pressure and pulse should be taken at rest while sitting. Physical exam should be performed at baseline, on Day 1 of each cycle, and at the treatment discontinuation visit. A focused physical exam may be

performed if clinically indicated at Cycle 1 Day 8 and 15.
[5]Height only needs to be obtained at baseline.
[6]AE assessment using CTCAE v5. All TRAEs will be followed until resolution, return to baseline, or deemed clinically insignificant by the treating investigator, including those that occur during the 30-day period after treatment discontinuation. In addition, any SAE related to treatment occurring more than 30 days after treatment discontinuation will be followed until either resolution, return to baseline, or determination by the investigator that the event has become stable or irreversible.
[7]A new diary will be distributed on Day 1 of each cycle and collected on Day 1 of the next cycle. See Appendix 2 for a template of the Cabozantinib Drug Diary.
[8]CBC and differential includes: hemoglobin, hematocrit, leukocyte count, neutrophils (segmented and bands), lymphocytes, monocytes, eosinophils, basophils, and platelets. Serum chemistry includes: sodium, bicarbonate, potassium, calcium, magnesium, magnesium, phosphate, glucose, albumin, total protein, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin. In addition to the scheduled labs as indicated in the table, more frequent lab monitoring may be initiated by the investigator in the event of AEs.
[9]HCV RNA is obtained if hepatitis C virus antibody (HCV Ab) is positive. There is no need to repeat serology or RNA during the study.
[10]If hepatitis B virus core antibody (HBcAb) and surface antigen (HBsAg) at baseline are negative, no further testing is needed. If HBcAb+ and/or HBsAg+, HBV DNA should be obtained at baseline. If a patient is HBcAb+ and HBsAg- at baseline, HBsAg should be obtained every 2 cycles on study starting at cycle 3 and HBV DNA is obtained if HBsAg becomes positive. If a patient is HBcAb+ and HBsAg+, HBV DNA should be obtained every 2 cycles on study starting at cycle 3.
[11]These tests should be obtained at baseline (within 14 days prior to registration) and repeated every 2 cycles on study starting at cycle 3.
[12]EGD must be done within 6 months prior to study initiation to assess for and treat esophageal and gastric varices.
[13]Alpha fetoprotein (AFP) should be measured at baseline (within 14 days prior to registration). If abnormal at baseline, it should be measured on Day 1 of every 3 cycles starting at cycle 4, and at the treatment discontinuation visit.
[14]Disease assessment using multiphasic (four-phase) contrast CT or MRI of abdomen/pelvis, as well as CT chest with or without contrast should be done at baseline (within 28 days prior to registration), and every 9 weeks on treatment (every 3 cycles). If there is disease progression and the patient continues on treatment beyond progression, repeat imaging must be performed 4 weeks later to confirm progression. As clinically indicated, bone scan and contrast imaging of neck may be obtained to monitor disease (see Section 13.3). For the treatment discontinuation visit, the most recent scans are used. For patients who come off study for toxicity, subsequent restaging scans will be requested and assessed at least every 4 months for up to 2 years from study start date to document the date of progression.
[15]Archival tumor tissue is acceptable (paraffin-embedded tumor core biopsy or surgical specimen). If archival tissue is not available, baseline core needle biopsy may be performed (if safe and feasible).
[16]Pre-treatment Blood will be collected and stored for correlative studies. Research blood will be collected on Cycle 1 Day 1 and Day 8, as well as Cycle 2 Day 1.
[17]Informed consent/HIPAA, medical/smoking history, AE/medication assessment, physical exam/ECOG, and assessment of inclusion/exclusion criteria are completed within 28 days prior to registration. Baseline lab investigations are completed within 14 days prior to registration, including pregnancy test for women of child-bearing potential (WOCP) and AFP. Baseline imaging for disease assessment may be obtained within 28 days prior to registration.
[18]Cycle 1 day 1 testing need not be repeated if completed within 7 days prior.
[19]The treatment discontinuation visit should occur 30 days (+7 days) after the last dose of cabozantinib or pembrolizumab (whichever is latest). Most recent scans are used for the treatment discontinuation visit. Note: if a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial

treatment, the treatment discontinuation visit must occur before the first dose of the new therapy and AEs occurring until that point will be collected.
[20]All patients who were treated will be followed for survival every 4 months with phone calls for up to 3 years from study start date. Patients who came off study for toxicity will be followed for progression with visits or by request of outside medical records every 4 months up to 3 years from study start date, where progression will be assessed by requesting and obtaining subsequent restaging scans. Subsequent anti-neoplastic therapy will be collected if available.
Abbreviations: C, cycle; q2C, every 2 cycles.

11.0 STUDY ASSESSMENTS

11.1 Baseline/screening evaluations

Within 28 days prior to registration:

- Informed consent and HIPAA authorization will be obtained according to ICH/GCPguidelines prior to performing any study-specific procedures.
- Medical and smoking history will be recorded.
    - Medical history must include all active conditions and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.
- Disease details and treatments will be recorded.
    - This information will include: BCLC stage at diagnosis and current BCLC stage, and all prior cancer treatments (e.g. surgery, ablation, liver-directed therapy).
- Assessment of vital signs, physical examination, assessment of ECOG status, weight, height, baseline AEs and medications.
    - Medication history will include any prior medication use within 28 days before starting on study, including indication and any protocol-related washout requirement. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.
- Assessment of eligibility based on inclusion/exclusion criteria by treatment investigator (Section 5.0).
- Multiphasic contrast CT or MRI of abdomen/pelvis and CT chest with or without contrast for baseline disease assessment, as well as confirmation of measurable disease and at least 1 appropriate target lesion per RECIST v1.1. As clinically indicated, bone scan and contrast-imaging of neck may be obtained.
- Archival tissue will be requested if available. If archival tissue is not available, an optional fresh core biopsy may be performed (if safe and feasible).
    - For patients who had prior next-generation gene sequencing analysis of their tumor, the gene sequencing assay results will be requested.

Within 14 days prior to registration:

- CBC with differential (including hemoglobin, hematocrit, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets).
- Serum chemistry (including sodium, bicarbonate, potassium, calcium, magnesium, magnesium, phosphate, glucose, albumin, total protein, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).

- PT/INR and PTT.
- Lactate dehydrogenase (LDH)
- Pregnancy test by serum HCG (for women of child-bearing potentialonly).
- Alpha fetoprotein.

11.2 On study evaluations

Patients will be monitored for response to therapy (disease assessment, see Section 13.0) every 9 weeks (every 3 cycles), and for AEs continuously from the time of consent to 30 days after discontinuation of drug.

Cycles 1 Days 1, 8, 15

NOTE: Cycle 1 day 1 testing does not need to be repeated if completed within 7 days prior.

- Assessment of vital signs, physical examination, ECOG status, andweight.
- Assessment of AEs and medications. Medication start/stop dates and indication for use during the study will be recorded.
- CBC with differential (Days 1 and 15 only) (including hemoglobin, hematocrit, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets).
- Serum chemistry (Days 1 and 15 only) (including sodium, bicarbonate, potassium, calcium, magnesium, magnesium, phosphate, glucose, albumin, total protein, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).
- PT/INR, PTT(Day 1 only).

Cycles 2+ Day 1 (± 2 days):

- Throughout the trial, patients will complete the Cabozantinib Drug Diary (Appendix 2). This will be collected on Day 1 of each cycle.
- Assessment of vital signs, physical examination, ECOG status, andweight.
- Assessment of AEs and medications. Medication start/stop dates and indication for use during the study will be recorded.
- CBC with differential (including hemoglobin, hematocrit, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets).
- Serum chemistry (including sodium, bicarbonate, potassium, calcium, magnesium, magnesium, phosphate, glucose, albumin, total protein, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).
- PT/INR, PTT.

Every 2 cycles starting at Cycle 3 Day 1 (± 2 days):

- HBsAg (for patients who are HBcAb+ and HBsAg- at baseline), or HBV DNA (for patients who are HBcAb+ and HBsAg+ at baseline). If HBsAg becomes positive on study, HBV DNA should then be followed.
- TSH with reflex T4, cortisol, amylase, lipase.
- Urinary protein to creatinine ratio.
- EKG.

At the end of every 3 cycles (prior to Cycles 4, 7, 10, etc):

Multiphasic contrast CT or MRI of abdomen/pelvis, as well as CT chest with or without contrast for disease assessment as per RECIST v1.1. The same imaging technique should be used throughout the study. If there is disease progression and the patient continues treatment beyond progression, repeat imaging must be obtained 4 weeks later to confirm PD. As clinically indicated, bone scan and contrast-imaging of neck may be obtained.

Every 3 cycles starting at Cycle 4 Day 1 (± 2 days):

- Alpha fetoprotein level (if abnormal at baseline).

11.3 Assessment of safety parameters at baseline and during study treatment

Laboratory assessments

Blood samples will be collected at the time points specified and analysed in a laboratory facility at the local investigational site. In the event of AEs or lab abnormalities, additional tests and/or more frequent lab monitoring may be obtained at the discretion of the treating investigator.

Safety laboratory assessment at baseline and on treatment must include at least the following parameters. Also see Appendix 3.

At baseline and every cycle	
Complete blood count	Hemoglobin, hematocrit, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets
Serum chemistry	Sodium, bicarbonate, potassium, calcium, magnesium, magnesium, phosphate, glucose, albumin, total protein, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkalinephosphatase, total bilirubin. Glomerular Filtration Rate (GFR) will be estimated by the Cockcroft-Gault formula using serum creatinine values (see Appendix 7).
Coagulation	PT/INR, PTT
Miscellaneous	LDH (baseline only)
At baseline and every 2 cycles	
Hepatitis B virus	At baseline: HBcAb and HBsAg. On study: • HBsAg (for patients who are HBcAb+ and HBsAg- at baseline), or HBV DNA (for patients who are HBcAb+ and HBsAg+ at baseline). • If HBsAg becomes positive on study, HBV DNA should then befollowed.
Monitoring for immune toxicity	TSH with reflex T4, cortisol, amylase, lipase
Urine protein	Urinary protein to creatinine ratio
QTc	EKG

Assessment of other safety parameters

- *Physical examination, ECOG performance score*

  A physical examination will be performed at screening and at the time points specified in the Study Calendar.

  A full physical exam serves as a clinical tumor assessment and should include cardiopulmonary and abdominal examinations and an assessment of the mental and neurological status. Wherever possible, the same investigator should perform this examination.

  Measurement of height (in cm), body weight (in kg) and body temperature and the evaluation of the ECOG performance score will be performed at the time points specified in the Study Calendars.

- *Vital signs*

  Vital signs include blood pressure and pulse after resting and sitting for at least 5 minutes, respiratory rate, oxygen saturation, and temperature. These will be recorded at the screening visit and at the time points specified in the Study Calendar.

- *Demographics and history*

  Demographics (sex, birth date), information on smoking history, and pre-existing medical conditions will be collected during the screening visit.

  Information on the etiology of HCC, including history of HBV, HCV, alcohol abuse, non-alcoholic steatohepatitis, or other will be collected at the screening visit. Specifically, for patients known to have HBV or HCV, details on prior anti-viral therapy, dates of therapy and response will be recorded.

  The date of first diagnosis of HCC (month and year are sufficient) and tumor histology if prior pathology results are available will be reported in the CRF. Moreover, BCLC stage at initial diagnosis and current BCLC stage will be recorded, as well as the current number and locations of metastatic sites (liver, lung, lymph nodes, peritoneum, other), presence of vascular invasion (specify location). Previous treatments including surgery, catheter-based therapy, and radiotherapy will be documented, including start and end dates (month and year are sufficient) and the best response obtained (complete response, partial response, stable disease, progressive disease, unknown).

11.4 Evaluations at treatment discontinuation (at 30 days [+ 7 days] following last dose of cabozantinib or pembrolizumab)

- Collection of the Cabozantinib Drug Diary, if not previously collected.
- Assessment of vital signs, physical examination, ECOG status, and weight.
- Assessment of AEs and medications. Medication start/stop dates and indication for use during the study will be recorded.
- CBC with differential.

- Serum chemistry.
- PT/INR and PTT.
- Alpha fetoprotein.
- Most recent imaging will be used for the treatment discontinuation visit: multiphasic contrast CT or MRI of abdomen/pelvis, as well as CT chest with or without contrast. As clinically indicated, bone scan and contrast-imaging of neck may also beobtained.

11.5 Post-study follow-up

Subjects will return approximately 30 days after their last dose of cabozantinib or pembrolizumab (i.e. treatment discontinuation visit) to complete end-of-study assessments (see Section 11.4). Unused study drug will be returned by the subject. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the treatment discontinuation visit must occur before the first dose of the new therapy.

All treatment-related AEs will be followed until resolution, return to baseline, or deemed clinically insignificant by the treating investigator, including those that occur during the 30-day period after treatment discontinuation. Moreover, any known SAE attributed to study treatment that occurs more than 30 days after treatment discontinuation must be followed until either resolution, return to baseline, or determination by the investigator that the event has become stable or irreversible; all concomitant medications for these SAEs after 30 days from treatment discontinuation must also be recorded.

For patients who discontinue study treatment due to toxicities or reasons other than progressive disease, subsequent imaging, if available, will be requested every 4 months up to 2 years from study start date to document time of progression after coming off study. For patients who come off study due to progressive disease, patients will be followed for survival every 4 months up to 2 years from study start date (no scans will be required). Moreover, subsequent anti-neoplastic therapy receive after study discontinuation will be collected, if available.

12.0 CRITERIA FOR TREATMENT DISCONTINUATION

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 11.4 and 11.5.

A patient will be discontinued from study treatment under the following circumstances:

- Progressive disease (PD) as per RECIST v1.1 or the subject no longer experiences clinical benefit as determined by the investigator (see Section 12.1 for criteria for continuing treatment beyond progression).
- Unacceptable toxicities despite supportive therapy and dose reduction/modification.

- Discontinuation of pembrolizumab for recurrent grade 2 pneumonitis.
- An AE or intercurrent illness/condition or personal circumstance which, in the opinion of the investigator, places the participant at unnecessary risk from continued administration of study intervention.
- Any progression or recurrence of another malignancy, or any occurrence of another malignancy that requires active treatment.
- Constraints of this protocol are detrimental to the patient's health.
- Necessity for treatment with other anticancer agents or other treatment prohibited by protocol.
- TRAE that results in interruption of cabozantinib > 4 weeks and pembrolizumab > 12 weeks, unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy upon resolution of the toxicity and with agreement of the Study PI.
- Patient requests discontinuation.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (Appendix 8) during the course of the study and for 4 months after discontinuation of study treatment.
- Women who become pregnant or are breastfeeding.
- 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.
- Discontinuation of pembrolizumab may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 further cycles of cabozantinib and pembrolizumab beyond the date when the initial CR was declared.
- Completion of 2 years of therapy.
- Participant has any of the following non-overdose HECIs that are not reversible and manageable by therapy (see below). (Note: Temporary hepatic decompensation may occur in patients with cirrhosis exposed to TKIs.)
    - ALT >20 × ULN (confirmed within 1 week)
    - Drug-related total bilirubin >10 x ULN
    - CP score of > 8 points
    - Hepatic encephalopathy
    - Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to beimmune-related
    - Uncontrolled ascites
- Subject is lost to follow-up.

Patients who come off study should be evaluated at 30 days (+ 7 days) after the last dose of cabozantinib or pembrolizumab (whichever is latest). AE assessment and reporting for patients who discontinue study treatment are described in Section 16.3.2. Furthermore, subjects who come off study for reasons other than PD will be followed for progression, and all patients who come off study will be followed for survival every 4 months for up to 2 years from study start date.

12.1 Treatment beyond progression

Cases of pseudo-progression have been documented in certain tumor types treated with immune-oncology agents.[60] Patients with initial disease progression on imaging (i.e. PD by RECIST v1.1, iUPD by iRECIST, see Section 13.0) may be allowed to continue on study treatment if they meet all of the criteria below:

- Patient is tolerating treatment.
  - Note: Patients are allowed to continue beyond progression on monotherapy cabozantinib (any dose) or pembrolizumab if the other agent was previously discontinued due to toxicity.
- Patient is deriving clinical benefit from ongoing treatment as assessed by the investigator.
- Patient continues to meet eligibility criteria.
- Disease progression is asymptomatic and does not pose a risk of a serious complication (e.g. progression in vertebral metastasis expected to lead to fracture or cord compression with further growth).
- Patient has stable ECOG performance status and is not expected to decline in the nearfuture.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. radiation to CNS metastases).

Patients who meet the above criteria and continue study treatment beyond progression must sign a consent form to do so.

If a patient continues treatment beyond progression, repeat imaging will be obtained at 4 weeks to confirm PD (i.e. iCPD by iRECIST). If there is confirmed disease progression, it is generally recommended that the study treatment be discontinued. However, if the patient appears to be deriving clinical benefit from treatment and is clinically stable, treatment beyond confirmed PD may be continued with permission obtained from the PI. If disease appears stable and PD cannot be confirmed on subsequent scans (i.e. response remains iUPD), then the patient may continue on study as long as clinically stable. See Section 13.2 for iRECIST criteria. Table 12.1.1 provides guidance on treatment after radiologic evidence of PD.

Table 12.1.1. Imaging and treatment after first radiologic evidence of progressive disease.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with	No additional imaging required.	Not applicable

		Principal Investigator		
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

13.0 GUIDELINES FOR DISEASE EVALUATION

The primary endpoint of this study is ORR by RECIST v.1.1. Secondary endpoints include DCR by RECIST v1.1, as well as ORR and DCR by iRECIST. Response criteria will be assessed by a central radiology team (OncoRad) at the University of Washington.[60,61]

13.1 Tumor assessment by RECIST v1.1 (primary endpoint)

13.1.1 Definitions for measurable disease and target lesions

Criteria for target lesions

- Lesions that are ≥ 10 mm (long axis) on CT (slice thickness 5 mm or less) orMRI
- Lymph nodes must be ≥ 15 mm (short axis) on CT (slice thickness 5 mm or less) orMRI
- Up to 5 target lesions in total can be reported, and a maximum of 2 lesions perorgan
- Target lesions should be the largest and most reproducible lesions on repeatassessments
- Target lesions should be representative of all involvedorgans

Notes:
- The lymphatic system is considered one organ in RECIST v1.1. Therefore, a maximum of 2 lymph nodes that are classified as target lesions should be reported on the RECIST CRF.
- Lesions that were previously radiated or ablated cannot be target lesions unless there was subsequent radiographic progression at those sites.

Criteria for non-target lesions

- Any lesions that don't meet the criteria for target lesions or are above the reporting limit for target lesions
- All other sites of disease that are <10 mm (long axis) on CT or MRI
- Lymph nodes that are ≥10 to <15 mm in the short axis on CT or MRI
- Lesions truly non-measurable such as ascites, leptomeningeal disease, pleural and pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung
- Lesions that are not suitable for repeat measurement, e.g. abutting other structures or likely to coalesce with other lesions
- Multiple non-target lesions in the same organ should be reported as a single non-target lesion, e.g. multiple liver metastases

Note: The lymphatic system is considered one organ in RECIST v1.1. Therefore, multiple lymph nodes that are classified as non-target lesions should be reported as a single non-target lesion on the RECIST CRF.

Measurable disease

- Lesions that can be accurately measured in the longest dimension as ≥10 mm by CT scan, ≥20 mm by chest X Ray, ≥10mm by caliper on clinical exam. Malignant lymph nodes need to be ≥ 15 mm (short axis) on CT.

Non-measurable disease

- All other lesions that do not fit the criteria for measurable disease. All definitions are outlined in RECIST v1.1 reference.[61]

13.1.2 Definitions of response

12.1.2.1 Evaluation of response of target lesions

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

Partial response (PR): At least a 30% decrease in the sum target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least a 20% increase in the sum target lesions, taking as reference the smallest sum on study recorded since the treatment started, or the appearance of one or more new lesions. In

addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for PD, taking as reference the smallest sum diameters since the treatment started.

12.1.2.2 Evaluation of response of non-target lesions

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

Incomplete response/stable disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesion(s).

13.1.3 Evaluation of overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference the smallest measurements recorded since the treatment started to determine response and progression).

Target lesions	Non-target lesions	New lesion	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

13.1.4 Definitions for response evaluations

First documentation of response: The time between initiation of therapy and first documentation of PR or CR.

Duration of response: Duration of overall response - the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

Duration of overall complete response: The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

Duration of stable disease: The period measured from the time that stable disease is documented until the first date that progressive disease is objectively documented.

Time to progression: A measurement from the study enrollment until the criteria for disease progression are met (or death occurs), taking as reference the smallest measurements recorded since the therapy started.

Overall survival: The overall survival time for each subject is the number of days from the day of first treatment to the earlier of (1) death (from any cause) or (2) the last date of subject contact. If the survival time does not correspond to the subject's death, then it is treated as censored.

13.2 Tumor assessment by iRECIST (secondary endpoints)

To account for the possible unique pattern of immune-mediated tumor responses, evaluation by iRECIST will also be performed as secondary objectives. Below is a general summary of the iRECIST criteria. Please refer to Seymour et al. 2017 for the full iRECIST guidelines.[60] Responses assigned under iRECIST are designated with the prefix 'i' (immune).

13.2.1 Similarities and differences between iRECIST and RECIST v1.1

In iRECIST, the definitions are identical to RECIST v1.1 for the following:

- Measurable and non-measurable disease including nodal disease
- Numbers and sites of target lesions
- Calculation of sum of diameters (SoD)
- CR, PR, SD, duration
- Confirmation of CR or PR (for non-randomized trials)
- PD for target and non-target lesions

However, the management of new lesions and determination of progression differ:

- For target lesions, the first PD by RECIST v1.1 is iUPD (immune unconfirmed PD).
- iUPD must be confirmed 4-8 weeks later by imaging.
    - iCPD (immune confirmed PD) is established if there is a further increase in SoD of target disease from iUPD of at least 5mm.
    - If there is subsequent iPR, iCR, or iSD (determined by RECIST v1.1 compared to baseline), then the iUPD date is ignored and the status is reset.
    - If there is no change detected from iUPD, then the timepoint response remains iUPD

- Treatment past iUPD is considered only if the patient is clinically stable.
- iUPD can be assigned multiple times as long as iCPD is not confirmed at the nextassessment.
- Assignment of non-target lesions follows similar rules.
- New target lesions are recorded separately and not included in SoD of target lesions identified at baseline; the sum of diameters for the new target lesions is determined.
    - Appearance of new lesions results in iUPD, which requires confirmation at 4-8 weeks.
    - iCPD is assigned if, on next imaging, additional new lesions appear, there is an increase in new lesions (at least 5mm), or appearance of new lesions.

13.2.2 Timepoint response using iRECIST

Target lesions	Non-target lesions	New lesions	Timepoint response with no previous iUPD in any category[1]	Timepoint response with previous iUPD in any category
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/ non-iUPD	No	iPR	iPR
iPR	Non-iCR/ non-iUPD	No	iPR	iPR
iSD	Non-iCR/ non-iUPD	No	iSD	iSD
iUPD with no change, or with decrease from last timepoint	iUPD with no change, or decrease from last timepoint	Yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and have increased in size (>=5mm in the sum of diameters for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed by a further increase in size of non-target disease (does not need to meet RECIST v1.1 criteria for unequivocal progression)
iUPD	Non-iCR/ non-iUPD, or iCR	No	iUPD	Remains iUPD unless iCPD is confirmed by a further increase in SoD >=5mm; otherwise, assignment remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed by a further increase in previously identified target lesion iUPD in SoD >=5mm or non-target lesion iUPD
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD is confirmed by a further increase in previously identified target lesion iUPD in SoD >=5mm, previously identified non-

				target iUPD, or increase in size of number of new lesions previously identified
Non-iUPD or progression	Non-iUPD or progression	Yes	iUPD	Remains iUPD unless iCPD is confirmed by increase in size or number of new lesions previously identified

Adapted from Seymour et al. 2017.[60]
[1]Preivously identified in assessment immediately before this timepoint.
Target lesions, non-target lesions, and new lesions defined according to RECIST v1.1. In the absence of pseudoprogression, RECIST v1.1 and iRECIST categories for CR, PR, SD would be the same.
Abbreviations: "I" indicates immune responses assigned using iRECIST; iCR, complete response; iPR, partial response; iSD, stable disease; iUPD, unconfirmed progressive disease; non-iCR/non-iUPD, criteria for neither CR not PD have been met; iCPD, confirmed progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

13.3 Methods of measurement

Imaging-based evaluation is required for assessment of response to study treatment. The same imaging modality must be used throughout the study to measure disease.

Imaging: Only CT or MRI are acceptable forms of imaging for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols. All other forms of assessment, including chest x-ray, ultrasound, PET without diagnostic CT, and endoscopy, will not be used for disease measurement.

As per NCCN guidelines for the management of hepatocellular carcinoma, it is recommended that disease assessment be performed using multiphasic contrast CT or MRI of abdomen/pelvis, as well as CT chest with or without contrast. As clinically indicated, bone scan and contrast-imaging of neck may be obtained to monitor disease.
(Principles of Imaging, NCCN guidelines version 1.2019, Hepatocellular Carcinoma, https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf)

Alpha fetoprotein (AFP): AFP may be elevated in patients with hepatocellular carcinoma and/or cirrhosis. AFP should be obtained at screening for all patients. If abnormal at baseline, it should be obtained on Cycle 1 Day 1, and every 3 cycles afterwards until treatment discontinuation.

Cytology and histology: Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

Clinical examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

14.0 DRUG INFORMATION

Drug supplies will be labeled in accordance with regulatory requirements. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies must be stored in a secure, limited-access location, and may not be used for any purpose other than that stated in the protocol.

14.1 Cabozantinib

14.1.1 Composition and formulation

Cabozantinib tablets are supplied by Exelixis as film-coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib. They also contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 14.1.1.1.

Table 14.1.1.1. Cabozantinib tablet components and composition

Ingredient	Function	% w/w[1]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

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

14.1.2 Storage and handling

Refer to the Pharmacy Manual for full details on storage and handling of cabozantinib. Cabozantinib tablets should be stored according to the temperature range listed on the product label and should not be crushed or chewed. Patients should store the cabozantinib capsules in the original package provided and be instructed to keep all medication out of reach of children.

14.1.3 Administration

Subjects will receive cabozantinib 20 mg oral tablets and will start at a dose of 40 mg once daily. Dosage will be adjusted for toxicity (see Section 9.0).

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.

14.1.4 Treatment accountability

Patients are required to complete the Cabozantinb Drug Diary and return all drug bottles and unused tablets. The number of tablets dispensed and returned will be recorded and reconciled with the diary.

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

14.2 Pembrolizumab

14.2.1 Formulation and preparation

Pembrolizumab is supplied by Merck in solution form for injection at a concentration of 100 mg/4 mL. Please refer to the Pharmacy Manual for a comprehensive description of pembrolizumab preparation.

14.2.2 Storage and handling

Pembrolizumab must be stored securely under storage conditions as specified on the drug label and in the Pharmacy Manual.

14.3.3 Treatment accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies of pembrolizumab received from Merck, the amount dispensed and returned for each subject, 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 as per institutional policy. It is the responsibility of the investigator or designee to arrange for disposal of all empty containers, following the procedures for proper disposal as per applicable federal, state, local and institutional guidelines. Records of disposed drug must be kept.

15.0 BIOLOGICAL CORRELATIVE STUDIES

15.1 Tissue collection

Archival tumor tissue will be requested, collected, and stored ambiently if available. If archival tissue is not available, an optional fresh tumor biopsy may be performed if safe and feasible. Tissue will be stored for future correlative studies in order to assess correlations of biomarkers with efficacy from cabozantinib and pembrolizumab in HCC patients.

If applicable, archival tumor tissue will be obtained from paraffin embedded specimens. Two unstained slides will be required for correlative studies. For patients undergoing fresh tumor biopsy, 3 cores will be obtained to assure at least 50 mm^2 of tissue needed for analysis (see below).

In addition, research blood will be collected on Cycle 1 Day 1and Day 8 and Cycle 2 Day 1.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be safely stored at -70oC until they are assayed.

Samples will be retained at the University of Washington for a maximum of 15 years after the last patient visit for the study, or for a shorter period if imposed by the IRB. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development cabozantinib and pembrolizumab in HCC. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section. The correlative studies will be planned as detailed in sections15.2-15.4.

15.2 Immunohistochemistry (IHC)

Archival or fresh tumor tissue will be immunophenotyped by a comprehensive multiplex IHC assay in the Immunopathology Core at Fred Hutchinson Cancer Center in order to detect a range of immune cell subsets and their distribution in tumor, including CD8+ and CD4+ effector T cells, regulatory T cells, macrophages, myeloid derived suppressor cells.

In addition, IHC will also be performed to assess the intratumoral levels of MET and various markers of immune checkpoint pathways (e.g. PD-1/PD-L1/PD-L2, CTLA-4, LAG3, TIM3). The intratumoral immune profile will be characterized and correlated with response to treatment.

15.3 RNA sequencing

Archival or fresh tumor tissue will be analyzed by RNA sequencing and gene set enrichment assay to explore immune gene expression signatures (e.g. IFN-g signature, tumor inflammation signature) and activated or suppressed cell pathways that might predict response to cabozantinib and pembrolizumab. Moreover, the mutational profile and T cell receptor clonality profile of tumors will be assessed. Signatures associated with tumor response will be explored.

15.4 Flow cytometry and cytokine assays

Peripheral blood (at baseline, Cycle 1 Day 8, Cycle 2 Day 1) will be analyzed by flow cytometry for immune cell subpopulations (e.g. CD8+/CD4+/regulatory T cells, myeloid derived suppressor cells). Furthermore, serum at the same timepoints will be assayed by the Luminex® cytokine panel. Changes in immune cell subsets and cytokine profiles in response to cabozantinib and pembrolizumab will be assessed and correlated with treatment outcomes.

16.0 ADVERSE EVENT ASSESSMENT AND REPORTING

The safety of cabozantinib and pembrolizumab will be evaluated and recorded. Specifically, these are the safety endpoints of interest:

- Type, incidence, and severity grade (as defined by NCI CTCAE v5) of AEs and SAEs, as well as relatedness of AEs/SAEs to cabozantinib, pembrolizumab or both;
- AEs/SAEs leading to dose reduction;
- AEs/SAEs leading to permanent treatment discontinuation;
- Causes of death.

16.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal vital signs, ECG, physical examination, and laboratory test results will be recorded as AEs if they are CTCAE v5 grade 3 or above, require clinical intervention, or are otherwise judged clinically relevant by the investigator.

Worsening of the underlying disease is not considered an AE; however clinical events associated with worsening of disease may be reportable as AEs, including the new onset of or increase in pain.

Serious adverse event (SAE): The SAE definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening (i.e. in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
    - Note: while most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
        - Events that occurred during the screening period after the patient signed the consent form but before initiation of study treatment (however, events related to screening procedures should be reported as SAEs);
        - Elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (however, SAEs must be reported for any surgical complication resulting in unexpected prolongation of the hospital admission);
        - Events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g. ER visit with diagnosis of urinary tract infection with discharge home on oral antibiotics);
        - Hospitalizations that are planned for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site) will not be recorded as SAEs (however, any event that requires prolongation of a planned hospitalization will be recorded as an SAE).
- Results in persistent or significant disability or incapacity:
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed.
    - Examples of IMEs: intensive treatment in the ER or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.
- Is a new cancer (other than HCC);
- Is associated with an overdose.

Unexpected: An AE that is not listed in the investigator's brochure describing the risks of the study drug, or is not listed at the specificity or severity that has been observed.

Severity of AE: The severity of AEs will be classified according to the NCI CTCAE v5, which describes grades of severity from 1 (mild) through 5 (fatal).

16.2 Attribution to study treatment

Assessment of the relationship or relatedness of an AE to study treatment (cabozantinib, pembrolizumab) or protocol procedure will be performed by the investigator who is a qualified physician, using the respective Investigator's Brochures as a references. Relevant factors for this determination include exposure history, temporal relationship, reaction to de-challenge or re-challenge, and confounding factors such as concomitant medication, concomitant diseases, and relevant history.

The relationship to study treatment or procedure will be described by the following: *definite*, *probable*, *possible*, *unlikely*, or *unrelated*. For simplification of reporting, AEs may be grouped as:

- **Not Related (unlikely, unrelated):** an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;

- **Related (definite, probable, possible):** an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g. evidence such as de-challenge/re-challenge) or other clinical arguments to suggest a causal relationship.

Attribution to study drugs for abnormal liver function lab tests should be considered carefully in the context of oncology patients. There should be no evidence of biliary obstruction, such as elevated alkaline phosphatase, progression of malignancy, or other explanation (viral hepatitis, other hepatotoxic drugs).

16.3 Parameters of assessment for AEs and SAEs

AEs and SAEs must be assessed by the treating investigator and recorded based on the following parameters.

Parameter	Description	
CTCAE v5 grade	Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	Does AE meet the definition of an SAE? (see Section 16.1 for definition)	
Duration	Record the start and stop dates of the adverse event or ongoing. If less than 1 day, indicate the length of time.	
Action taken	Did the AE cause each of the study drugs to be: held, dose reduced, discontinued, no action taken?	
Relationship to study drug(s)	What is the relationship of the AE to each of the study drug: unrelated, unlikely related, possibly related, probably related, definitely related? (see Section 16.2)	
Treatment required	Was treatment required for the AE (e.g. antibiotic, supportive medication)?	
Outcome	Is AE: ongoing, improved, stable, worsened, resolved?	

16.4 Monitoring and recording AEs

16.4.1 Responsibility for adverse event monitoring

Investigators (principal investigator, sub-investigators) and appropriately qualified clinical research staff will review participants' treatment activity, clinical status, and safety information/AEs on an ongoing basis.

16.4.2 Time frame for AE monitoring

AEs will be monitored from the time of informed consent through 30 days following the final dose of cabozantinib or pembrolizumab (whichever is lates). AEs with an onset date prior to informed consent will be recorded only in the case of worsening of the AE during study participation. All AEs will be followed until resolution, return to baseline, or deemed clinically insignificant by the treating investigator, even if they occur after treatment discontinuation for up to 30 days (or until the patient starts subsequent anticancer therapy, whichever is earliest).

SAEs of any cause will be monitored from the time of informed consent through 30 days and SAEs attributed to study procedure or treatment occurring more than 30 days after treatment discontinuation must be followed until either resolution, return to baseline, or determination by the investigator that the event has become stable or irreversible.

All pregnancies and exposure during breastfeeding will be monitored and reported from the time of treatment initiation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator. If pregnancy or lactation exposure occurs, the site must also contact the subject at least monthly and document the participant's status until the pregnancy has been completed or terminated.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

16.4.3 Laboratory data

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (e.g. dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

16.4.4 Recording AEs

All AEs, serious and non-serious, will be recorded in study-specific CRF forms. AE terms recorded on the CRF will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). For each AE, the investigator will provide the onset date, end date, severity grade (defined by NCI CTCAE v5), seriousness, action taken with the study drug(s), treatment required, and outcome (see Section 16.3). The list of medications administered for the treatment of the AEs will berecorded.

The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

16.5 Requirements for reporting AEs

16.5.1 SAE reporting

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following: (i) all SAEs that occur from the time of informed consent until 30 days after the treatment discontinuation, and (ii) all SAEs attributed to study treatment or procedure occurring more than 30 days after treatment discontinuation.

These SAEs and their follow-up must be reported within 24 hours to the Exelixis Drug Safety and Merck Global Safety:

- Any SAE occurring from the time of consent until treatment initiation if it causes the patient to be excluded from the trial, or if is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure
- Any SAE occurring on study regardless of causality from the time of consent until 30 days after treatment discontinuation
- Any SAE attributed to study treatment or procedure occurring more than 30 days after treatment discontinuation

All reportable SAEs must be sent to the following contacts within 24 hours of the PI's knowledge of the event:

- Exelixis: reports must be sent to Exelixis Drug Safety, drugsafety@exelixis.com or fax 650-837-7392
- Merck: reports must be sent to Merck Global Safety, fax 215-661-6229

The PI will perform adequate due diligence with regards to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis and Merck within 24 hours of the PI's receipt of the new information. Upon request, queriesmay be issued for follow-upinformation.

16.5.2 Reporting of pregnancy and lactation

Any pregnancy or lactation exposure that occurs from the time of treatment initiation through 120 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be immediately reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy, which must also be reported when available.

Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, stillbirth, or other disabling or life-threatening complication to the mother or newborn must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events

must be reported within 24 hours to Exelixis Drug Safety and Merck Global Safety (see Section 16.4.1 for contact information).

If a male participant impregnates his female partner, the Principal Investigator must be informed immediately and the pregnancy must be reported as well as described above.

16.5.3 Reporting of pembrolizumab overdose

For purposes of this study, an overdose of pembrolizumab is defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is attributed to an overdose of pembrolizumab, it must be reported as an SAE, even if no other seriousness criteria are met.

If an overdose of pembrolizumab is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 24 hours to Exelixis and Merck (see Section 16.4.1 for contact information).

16.5.4 Events of clinical interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229) and Exelixis Drug Safety (drugsafety@exelixis.com or fax 650-837-7392).

Any ECI occurring on study regardless of causality from the time of consent until 30 days after treatment discontinuation must be reported.

ECIs for this trial include:

1. Overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results (see Section 16.4.3);
2. Elevated AST or ALT ≥ 3X ULN and elevated total bilirubin ≥ 2X ULN and, at the same time, ALP < 2X ULN.

- Any ECI occurring from the time of consent until treatment initiation if it causes the patient to be excluded from the trial, or if is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure

16.5.5 Regulatory reporting

The Investigator will assess the expectedness of each related AE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) and the pembrolizumab Investigator's Brochure will be used as the reference documents for assessing the expectedness of the event with regards to cabozantinib and pembrolizumab, respectively.

- Expedited reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies.Specifically, requirements include reporting unanticipated problems involving risks to research participants or others to the FHCRC/Cancer Consortium IRB within 10 calendar days of the investigator's awareness of the problem. AEs that are (1) unexpected, (2) related or possibly related to the research, and (3) suggest that the research presents a greater risk of harm than was previously known or recognized, are among the unanticipated problems subject to these reporting policies. Exelixis and Merck reserve the right to upgrade the Investigator assessment of an SAE.
- Institutions shall promptly provide all information requested by Exelixis and Merck regarding all adverse events occurring during the conduct of the study.
- Exelixis and Merck will provide relevant product safety updates and notifications, as necessary.

Any AE that does not meet expedited reporting criteria may be reported at the time of continuing review.

17.0 STATISTICAL CONSIDERATIONS

17.1 Sample size calculation

The primary objective of this study is to evaluate the ORR in patients with advanced HCC treated with cabozantinib and pembrolizumab. This Phase 2 trial will be based on Simon's optimal two-stage design.

The null ORR is assumed to be 20%, which was the ORR (by RECIST v1.1) observed in the sorafenib-naïve group treated with nivolumab in the CheckMate 040 trial.[8] Early phase data with lenvatinib and pembrolizumab as first-line treatment showed an ORR of 35% in the expansion phase and an ORR of 42% in the overall patient population (DLT evaluation and expansion phase) using mRECIST criteria.[38] Therefore, the null hypothesis that the true ORR is 20% will be tested against a one-sided alternative that the assumed-true ORR with the tested combination is 38% by RECIST v1.1. The target assumed-true ORR of 38% is believed to adequately represent the potential activity of cabozantinib and pembrolizumab.

Using Simon's optimal two-stage design, 13 patients will be accrued in the first stage. If there are 2 or fewer patients with response (CR or PR) (an observed rate of 15% or less), the study will be suspended for lack of sufficient efficacy. Otherwise, 16 additional patients will be accrued for a total of 29 patients. The null hypothesis (of an ORR of 20%) will be rejected if 9 or more patients have a tumor response (CR or PR) out of 29 patients (an observed ORR of at least 31%). This design yields a type I error rate of 0.10 and power of 80% when the true ORR is 38%.

An accrual period of 24 months and follow-up period of 12 months are anticipated. More than 29 patients may be screened and/or enrolled depending on screen fails or dropouts before starting treatment.

17.2 Statistical methods

The primary endpoint is ORR per RECIST v1.1, while secondary endpoints include ORR by iRECIST, ORR and DCR by iRECIST, median PFS, and median OS. Only patients who have been on treatment with both cabozantinib and pembrolizumab concurrently for more than 42 days in the first 3 cycles (i.e. received treatment for two-thirds of the cycle) will be included in the analysis of the primary endpoint. Patients who have received any duration of study treatment will be evaluable for safety.

Binary endpoints will be summarized by percentages and associated confidence intervals. ORR will also be represented by a waterfall plot. The distribution for survival times will be estimated using the method of Kaplan-Meier; associated landmark time percentages and the median value will be based on this. Confidence intervals for median values will use the Brookmeyer-Crowley method. Any toxicity with at least 5% prevalence has at least an 77% chance of being observed among 29 patients.

For the exploratory objectives, archival or fresh tumors from all patients will be analyzed by IHC, the presence of specific immune cell subsets and protein marker expression, as well as the staining pattern and location within tumors will be described. The frequencies of immune cell subset will be obtained from flow cytometry at various timepoints, and cell changes from baseline to post-treatment timepoints will be averaged across patients. The association between immune cell, biomarker expression, gene expression signature, or cytokine level with ORR will be evaluated using Spearman correlation, where $p<0.05$ is considered significant.

18.0 DATA AND SAFETY MONITORING PLAN

18.1 Trial monitoring

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered onthem.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC), and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

18.2 Data and safety review

Investigators will conduct continuous review of data and patient safety. At least monthly review meetings are required and will include: PI, data manager, study coordinator, and other members as per the PI's discretion (e.g. sub-investigators, nurses).

Review of data and patient safety will be reviewed during these meetings, including:

- The number of patients enrolled in the protocol
- Any significant toxicities experienced by patients enrolled
- Dose modifications and responses observed

19.0 STUDY DOCUMENTATION AND RECORD-KEEPING

19.1 Investigator's files and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, any other records required under the Protocol, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; original laboratory, ECG, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of (a) 2 years following the marketing application approval date for the study treatment in the indication being investigated, or (b) 2 years after the investigation is completed or discontinued, or (c) for a period of time consistent with local regulatory requirements, whichever is longest. After that period, the documents may be destroyed subject to local regulations with prior written permission from Exelixis/Merck. If the investigator wants to assign the study records to another party or move them to another location, Exelixis/Merck must be notified in advance.

19.2 Source documents and background data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

19.3 Audits and inspections

The investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Exelixis or Merck Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

19.4 Case report forms

For enrolled subjects, only data from the procedures and assessments required by the CRFs should be entered on the appropriate CRF. Other are recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the

investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

20.0 PROTOCOL MODIFICATIONS

Protocol modifications or amendments must be reviewed and approved by Exelixis and Merck prior to implementation. All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (e.g. change in monitor or change of telephone number).

21.0 TERMINATION OF STUDY

At any time, the study may be terminated prior to completion of planned enrollment and achievement of objectives if there is evidence that the study regimen is not tolerable at the lower dose limits stated in the protocol, or if interim data analysis demonstrates lack of efficacy of study treatment. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

Upon study termination, the investigator shall cease enrolling subjects into the study and shall discontinue conduct of the study as soon as is medically practicable. The IRB will be notified about the completion or early termination of the trial.

22.0 ETHICAL ASPECTS

22.1 Local regulations

The study must fully adhere to the principles outlined in ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research.).

22.2 Institutional review board/ethics committee

This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC approval to Exelixis and Merck (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

22.3 Confidentiality of trial documents and subject regions

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

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

23.0 PUBLICATION OF DATA

The PI holds the primary responsibility for publication of the study results, provided that the PI will provide Exelixis and Merck with a copy of any proposed publication or release:

- (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and
- (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts and also comply with any provisions regarding publication that are agreed to between the University of Washington and Exelixis and Merck in the Clinical Trial Agreement related to this study.

24.0 APPENDICES

Appendix 1: Abbreviations and definitions

Abbreviation or term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC	area under the curve
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CI	confidence interval
CMV	Cytomegalovirus
CR	complete response
CRF/eCRF	case report form/electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSMC	data and safety monitoring committee
DVT	deep venous thrombosis
EBV	Epstein-Barr virus
eDC:	Electronic Data Capture. A computer database where clinical trial data are entered and validated.
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
Enrollment:	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter:	Patients entered into a trial are those who sign the informed consent form directly.
ERB/IRB	ethical review board / institutional review board
FFPE	formalin-fixed, paraffin-embedded
GCP	good clinical practice
GFR	glomerular filtration rate
GLP	good laboratory practice
GI	gastrointestinal
Hb	hemoglobin
HBeAb	hepatitis B e-antigen antibody
HBeAg	hepatitis B e-antigen antigen
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
i (prefix)	immune
IB	investigator's brochure
ICF	informed consent form

iCPD	immune confirmed progressive disease
IHC	immunohistochemistry
INR	international normalized ratio
Investigational product (IP):	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
irAE	immune-related adverse event
IRB	institutional review board
iUPD	immune unconfirmed progressive disease
IV	intravenous
LMWH	low molecular weight heparin
NSAIDS	non-steroidal anti-inflammatory drugs
MI	myocardial infarction
MRI	magnetic resonance imaging
OS	overall survival
ORR	objective response rate
PI	principal investigator
PD	progressive disease
PD-1	programmed cell death 1
PE	physical exam
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PPES	palmar-plantar erythrodyesthesia syndrome
PR	partial response
PTT	partial prothrombin time
QTc	corrected QTc interval (QTcF: QTc calculated by Fredericia formula)
RECIST	Response Evaluation Criteria In Solid Tumors
iRECIST	immune RECIST
mRECIST	modified RECIST
RBC	red blood cell
Reporting database:	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
Re-screen:	To screen a patient who was previously declared a screen failure for the same study.
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
Screen:	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
Screen failure:	Patient who does not meet one or more criteria required for participation in a trial.
SD	stable disease

TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
UPCR	urine protein to creatinine ratio
ULN	upper limit of normal
WBC	white blood cell
WOCP	women of child-bearing potential

Appendix 2. Cabozantinib Drug Diary

Today's Date: _____ Participant Study ID: _____

Participant Initials:_____ Cycle Number: _____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle (21 days).
2. You will take 40 mg of Cabozantinib (2) x (20 mg pills) once a day. Or 20 mg of Cabozantinib if dose reduced (1) x (20 mg pill).
   - Cabozantinib must be taken daily on an empty stomach. You must not to eat for at least 2 hours before and at least 1 hour after taking Cabozantinib.
   - Take your Cabozantinib dose at approximately the same time every day.
   - Cabozantinib pills should be swallowed whole with at least 8 ounces of water.
3. Record the date, the number of pills you took, and the time that you took them.
4. If you have any comments or notice any side effects, please record them in the comments column.
5. Please bring your pill bottle and this form to your physician when you go to your next appointment.
6. Please record missed or skipped doses. Do not share your drug supply. Wash your hands after touching the pills.
   - 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.
7. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges, star fruit, and their products should be avoided.

Date	**Day**	**DOSE**		**Comments**
		Number of Pills Taken	Time dose was taken	
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			

RG1007034	10			

	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	Participant's Signature:_____ Date: _____			
	Physician's office will complete this section: Number of tablets dispensed:_____Date of pills dispensed: _____ Participant's planned daily dose: _____ Total number of pills taken this month: _____ Has the patient missed any study medication? ☐ Yes ☐ No Comments:_____ Study Personnel Signature:_____Date: _____			

Medical EMERGENCY: 911 (such as chest pain, seizure, sudden shortness of breath, etc.)

Research Coordinator:_____/ Weekday Pager Number: _____
24-hour EMERGENCY pager: 206-598-6190

Appendix 3: Clinical laboratory tests

Hematology (at screening and on study) Hemoglobin Hematocrit Leukocytes (WBC) Neutrophils (segmented and bands) Lymphocytes Monocytes Eosinophils Basophils Platelets	**Serum chemistry** (at screening and on study) Sodium Bicarbonate (CO2) Potassium Calcium Magnesium Phosphate Glucose Albumin Total protein Blood urea nitrogen (BUN)
	Creatinine Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Total bilirubin
Coagulation (at screening and on study) International normalized ratio (INR) Partial thromboplastin time (PTT)	**HBV/HCV status** At screening: - HCV Ab (if positive, obtain HCV RNA) - HBcAb, HbsAg (if either or both are positive, obtain HBV DNA) On study: - HBcAb+ and HBsAg- at baseline: obtain HBsAg every 2 cycles starting at cycle 3 (and HBV DNA if positive) - HBcAb+ and HBsAg+ at baseline: obtain HBV DNA every 2 cycles starting at cycle 3
Other immune-related AE monitoring (at screening and every 2 cycles on study starting at cycle 3) TSH, free T4 and T3 Cortisol Amylase Lipase	**Urine protein** (at screening and every 2 cycles starting at cycle 3) Urine protein to creatinine ratio
Tumor marker (at screening and every 3 cycles starting at cycle 4) Alpha fetoprotein	**Serum pregnancy test** (women of childbearing potential only) at screening only

Appendix 4: Strong inducers and inhibitors of CYP3A

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9.

If possible, strong inducers of CYP3A4 (see below) should be avoided and substituted by alternative medications at the discretion of the treating physician. If they must be used, the patient must be on a stable dose.

Strong inducers of CYP3A: apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacafotor, mitotane, phenobarbital, phenotyoin, primidone

If possible, strong inhibitors of CYP3A4 (see below) should be avoided and substituted by alternative medications at the discretion of the treating physician. Grapefruit or grapefruit juice should be avoided.

Strong inhibitors of CYP3A: atazanavir, boceprevir, clarithromycin, cobicistat and cobicista containing coformulations, darunavir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, mifepristone, nefazodone, nelfinavir, ombitasvir-paritaprevir-ritonavir, ombitasvir-paritaprevir-ritonavir plus dasabuvir, posaconazole, ritonavir and ritonavir containing coformulations, saquinavir, telaprevir, telithromycin, voriconazole.

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

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

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

Appendix 5: ECOG performance status scale

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours.
3	Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours.
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair.

Appendix 6: Child-Pugh score calculation for cirrhosis mortality

Parameter	Point		
	1	2	3
Total bilirubin	<2 mg/dL (<34.2 umol/L)	2-3 mg/dL (34.2-51.3 umol/L)	>3 mg/dL (>51.3 umol/L)

Albumin	>3.5 g/dL (>35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (<28 g/L)
INR	<1.7	1.7-2.2	>2.2
Ascites	Absent	Easily controlled	Poorly controlled
Encephalopathy[1]	None	Grade 1-2	Grade 3-4

[1]Encephalopathy grades:
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Child-Pugh score	Class	1-year survival (%)	2-year survival (%)
5-6	A	100	85
7-9	B	80	60
10-15	C	45	35

Sources:
Child CG and Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Philadelphia: Saunders 1964:50-64.
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Appendix 7: Cockcroft-Gault equation for determining creatinine clearance (CrCl)

The Cockcroft-Gault equation is to be used for calculating CrCl from local laboratory results.

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in umol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (umol/L)}$$

Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Appendix 8: Highly effective methods of contraception

- Combined oral contraceptive pill and mini-pill
- NuvaRing®
- Implantable contraceptives
- injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch for women <90 Kg (<198 pounds)
- Bilateral tubal occlusion or hysterectomy with bilateral salpingo-oophorectomy
- Vasectomy

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