Document Coversheet

Study Title: Phase II Clinical Trial Evaluating Cabozantinib and Pembrolizumab in Metastatic Pancreatic Cancer

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COVER PAGE

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TITLE: Phase II Clinical Trial Evaluating Cabozantinib and Pembrolizumab in Second-Line Therapy for Metastatic Pancreatic Adenocarcinoma

Short Title: Cabozantinib and Pembrolizumab in Metastatic Pancreas

PROTOCOL FACE PAGE FOR
MCC INTERVENTIONAL THERAPEUTIC PROTOCOL

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Pembrolizumab [MK-3475, Keytruda; Merck]

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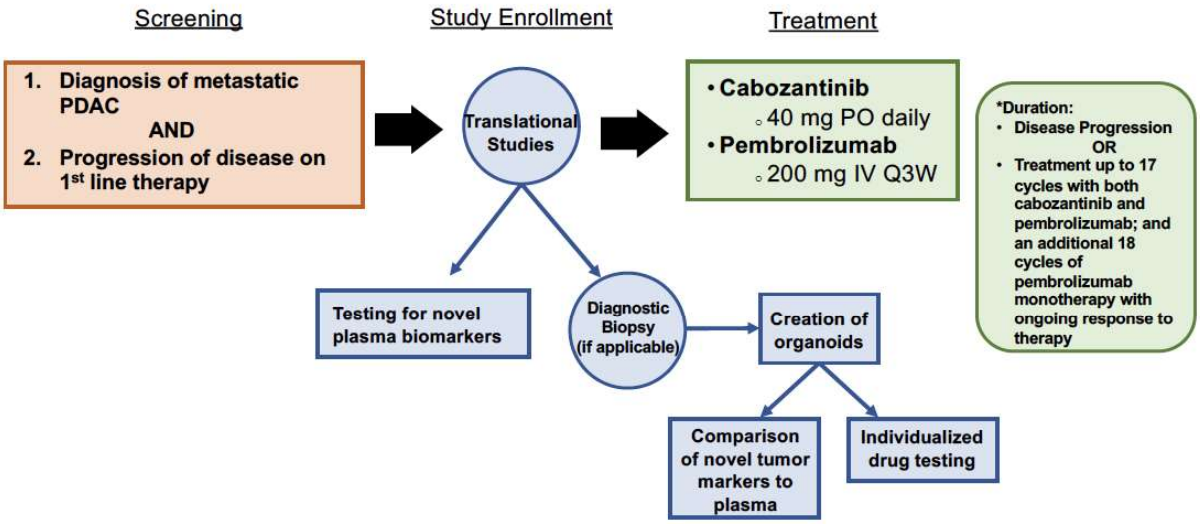
Protocol Type with Version # / Version Date: Original Protocol / 12.April.2021
Revision 1 / 27.October.2021
Amendment 1 / 04.August.2022
Amendment 2 / 27.March.2023

Protocol Development History – Original Version to Current Version, w/ major Summary of Changes noted	
Original Protocol	MCC protocol draft version dated 12APR2021 (Protocol file name 120220 from sponsor).
5/7/2021	PRMC Initial Full Review of the original protocol, pvd 12APR2021. *Resolution*: Full approval.
7/9/2021	Initial coverage analysis received from UKHC Central Research Support Office.
7/14/2021	IRB review of 12APR2021 protocol (initial review). *Resolution:* Edits required from initial IRB review. IRB Approval was obtained on 09/02/2021 for the revised 12APR2022 protocol
8/29/2021	FDA IND status determination.
Revision 1 10/27/2021	Protocol was modified slightly in response to IRB critiques (clarifying 4-months is the window to report pregnancy after last dose); clarification that research samples for the correlatives will be collected under a biospecimen sample collection protocol. New protocol version date, 27OCT2021. This revised protocol also contains a new pill diary for Cabozantinib (new Appendix B); added clinicaltrials.gov identifier (cover page); clarifications re: urinalysis and aPTT tests (addresses questions re: Medicare coverage analysis). *Resolution*: Revision 1 protocol approved by IRB (11/23/2021).
12/22/2021	**Open to Accrual**
Amendment 1 04AUG2022	The protocol version date 27OCT2021 was modified to create Amendment 1, version dated 04AUG2022. Protocol edits are as follows: clarify 3.2.26 exclusion re: cavitating pulmonary lesions; clarify 3.2.27 exclusion criterion, invading blood vessels and encasement; and, clarify window for ECOG PS as within 2 weeks (sections 3.1.4, 4.3.3). Other minor updates in this amendment: trial opening date date trial (added above); noted the IND exemption from the FDA (page 1); text added to clarify language regarding emerging new first-line therapies (Schema); noted radiologist, affiliation address for imaging RECIST reads (Pg 1, 12.2.2, and 12.2.3).
Amendment 2 **27MAR2023**	The 04AUG2022 protocol was revised to correct the reporting of concomitant medications (S11 Study Calendar was clarified to align with Section 8.1). The Key Personnel (cover page) was updated. New protocol version date is 27MAR2023.
	Placeholder for future amendment
	Placeholder for future amendment

SCHEMA



NOTE: "1st line therapy" is defined as FOLFIRINOX and/or gemcitabine+abraxane, as well as other treatment regimens that are approved for 1st line therapy of metastatic pancreatic cancer during the course of this trial.

*One cycle of therapy is Q3W administration of pembrolizumab (200 mg IV) and cabozantinib (40 mg po daily).

*Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of cabozantinib beyond the date when the initial CR was declared.

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1. OBJECTIVES

1.1 Primary Objective

To measure progression-free survival (PFS), defined as the time from the start of treatment (Cabozantinib + Pembrolizumab combination) until the first documentation of disease progression or death due to any cause, whichever occurs first.

1.2 Secondary Objectives

1.2.1 To identify the proportion of participants with adverse events.

1.2.2 To measure the proportion of patients with overall response to therapy [*i.e.*, overall response rate (ORR): complete response (CR) + partial response (PR)] as determined by RECIST v1.10 via imaging conducted at 2 (+/- 1-2 weeks) months, 4 (+/- 1-2 weeks) months, and 6 (+/- 1-2 weeks) months and thereafter, imaging at q3 months or as clinically indicated.

1.2.3 To measure the proportion of patients with CR or PR at 1-year post-treatment initiation.

1.2.4 To measure 1-year overall survival (defined as time from start of treatment until up to 1-year post-treatment initiation or death from any cause).

1.3 Exploratory / Correlative Objectives

Patient-derived organoids will be developed from archival tumor tissue (if available) and exosomal lipids will be extracted from plasma samples to predict clinical response to Cabozantinib and Pembrolizumab. In order to participate in the correlative studies, patients will be consented on a separate biospecimen collection protocol. This separate consent allows collection of research blood and utilization of archival tumor tissue from patients enrolled in this clinical trial. Participation in correlative studies (organoids and lipids) is optional.

2. BACKGROUND

2.1 Pancreatic Cancer

Pancreatic cancer will soon become one of the deadliest cancers worldwide and routine diagnosis at advanced stages of disease complicates the ability to treat this devastating disease.[1] In fact, 60-80% of patients with pancreatic cancer have advanced disease at the time of diagnosis. Furthermore, >90% of patients develop metastatic disease and nearly all patients during their course of treatment become refractory to standard cytotoxic regimens.

2.1.1 Current Treatment

Current first-line standard of care therapy for metastatic pancreatic cancer is FOLFIRINOX [5-FU + leucovorin (LV) + oxaliplatin + irinotecan] or Gem-Abraxane (gemcitabine + nab-Paclitaxel). Each of these regimens are also indicated in the second-line as is the NAPOLI regimen (5-FU + LV + nanoliposomal irinotecan).

2.1.2 Immunotherapy in Pancreatic Cancer

Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have been successful against certain cancers but have shown marginal improvement for pancreatic cancer survival.[2-4]

2.2 Cabozantinib

Cabozantinib (XL184) is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, vascular endothelial growth factor receptor (VEGFR), AXL, and RET. Increased expression of MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). In addition, targets of Cabozantinib are implicated in promoting tumor-immune suppression including TYRO3, MER, and AXL [tumor-assisted macrophage (TAM) family kinases].

Cabozantinib capsules (140 mg) are approved in the US for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). Cabozantinib tablets (60 mg) are approved in the US, Europe, and other regions for advanced renal cell carcinoma (different patient populations depending on region; Cabozantinib® US PI). Based on the results from a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects who had received prior sorafenib, Cabozantinib tablets (60 mg) as a single agent have also been approved in the US, EU, and other regions for a hepato-cellular carcinoma indication.

Cabozantinib has also demonstrated encouraging clinical activity in other tumor indications: monotherapy in advanced urothelial carcinoma (Apolo et al [J Clin Oncol] 2016), in combination with ICIs in advanced urothelial carcinoma (Nadal et al 2018, Nadal et al 2017, Apolo et al [Ann Oncol] 2016), monotherapy in castration-resistant prostate cancer (Smith et al 2013, Smith et al 2014, Basch et al 2015), monotherapy or in combination with erlotinib in advanced non-small cell lung cancer (NSCLC) (Schöffski et al 2017, Neal et al 2016), monotherapy in RET-rearranged NSCLC (Drilon et al 2016), monotherapy in advanced TNBC (Tolaney et al 2017), monotherapy in advanced OC (Matulonis et al 2016, Vergote et al 2017), monotherapy in advanced EC (Dhani et al 2017; Mandilaras et al 2017), monotherapy in advanced GC (Schöffski et al 2017), in combination with panitumumab in CRC (Strickler et al 2016), and monotherapy in radioactive-iodine refractory DTC (Brose et al 2018, Cabanillas et al 2014, Cabanillas et al 2017). Cabozantinib has also been shown to be safe when combined with pembrolizumab in a phase I study for patients with renal cell carcinoma (Keeler et al 2019). More recently, a phase 3 randomized controlled trial for advanced renal cell cancer demonstrated the safety and efficacy of nivolumab combined with cabozantinib at 40 mg (Choueiri et al 2021). This cabozantinib dosage has been selected for the proposed pancreatic cancer clinical trial.

Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells (Apolo et al 2014) suggest that Cabozantinib promotes an immune-permissive environment through inhibition of immune-modulatory targets on immune cells. This might present an opportunity for synergistic effects from combination treatment with ICIs. The combination of Cabozantinib with ICIs may also provide a strategy to overcome resistance to ICI therapy. This is based on recent observations in clinical trials where re-treatment with an ICI in combination with Cabozantinib or a VEGFR-TKI that has a target profile similar to Cabozantinib resulted in reversal of prior ICI resistance in advanced UC and NSCLC patients (Nadal et al 2018, Leal et al 2017). These results suggest that combining ICIs with Cabozantinib may result in a tumor microenvironment that is conducive to re-sensitization to ICI therapy after prior progression on an ICI.

2.3 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in pancreatic cancer.

The planned dose of pembrolizumab for this study is 200 mg 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.
- 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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

2.4 Study Rationale and In Vivo Studies

Our previous studies revealed autonomous PD-1 expression and functionality on pancreatic cancer cells, organoids, and mouse models devoid of immune cells (**Fig. 1**).[5] Furthermore, we conducted a phospho-protein array which revealed activation of the oncogene MET by the PD-1/PD-L1 axis (**Fig. 2**). We then performed western blot assays and observed PD-1-dependent activation of MET (**Fig. 3**). These data suggested an avenue for directly targeting cancer cells by targeting both the immune checkpoint and MET pathways in combination.

Since PD-1 and MET are proteins targeted by current clinical drugs, Pembrolizumab and Cabozantinib, respectively, this novel multi-targeted combination is appropriate for human clinical trials. We observed synergistic killing from immune checkpoint inhibitors and Cabozantinib in pancreatic cancer cells and organoids (**Figs. 4** and **5**, below). Currently, human trials combining Cabozantinib with immune checkpoint inhibitors are being conducted in various cancer types, but none have investigated this combination in pancreatic cancer. Our goal is to administer this clinical combination with the goal to increase metastatic pancreatic cancer survival.

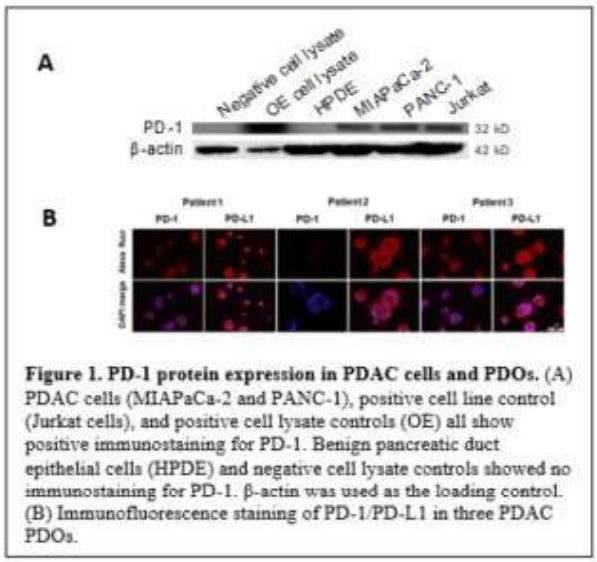


Figure 1. PD-1 protein expression in PDAC cells and PDOs. (A) PDAC cells (MIAPaCa-2 and PANC-1), positive cell line control (Jurkat cells), and positive cell lysate controls (OE) all show positive immunostaining for PD-1. Benign pancreatic duct epithelial cells (HPDE) and negative cell lysate controls showed no immunostaining for PD-1. β-actin was used as the loading control. (B) Immunofluorescence staining of PD-1/PD-L1 in three PDAC PDOs.

Activated PD-1/PD-L1 Pathways

Upregulated Targets	Fold Increase	FDA-Approved Drugs
HDAC-1	28.98	Vorinostat
Met	13.65	Cabozantinib
EGFR	6.4	Erlotinib

Figure 2. PD-1 upregulated pathways. Phospho Explorer Array, which measures the levels of over 200 phospho-specific antibodies and their corresponding total proteins, was performed to determine activated signaling pathways following exposure of PDAC cells to PD-L1 (1ug/ml). The phospho-protein array revealed a greater than 2.0-fold increase in the expression of the active form of the listed oncogenic proteins which are targeted by FDA-approved drugs.

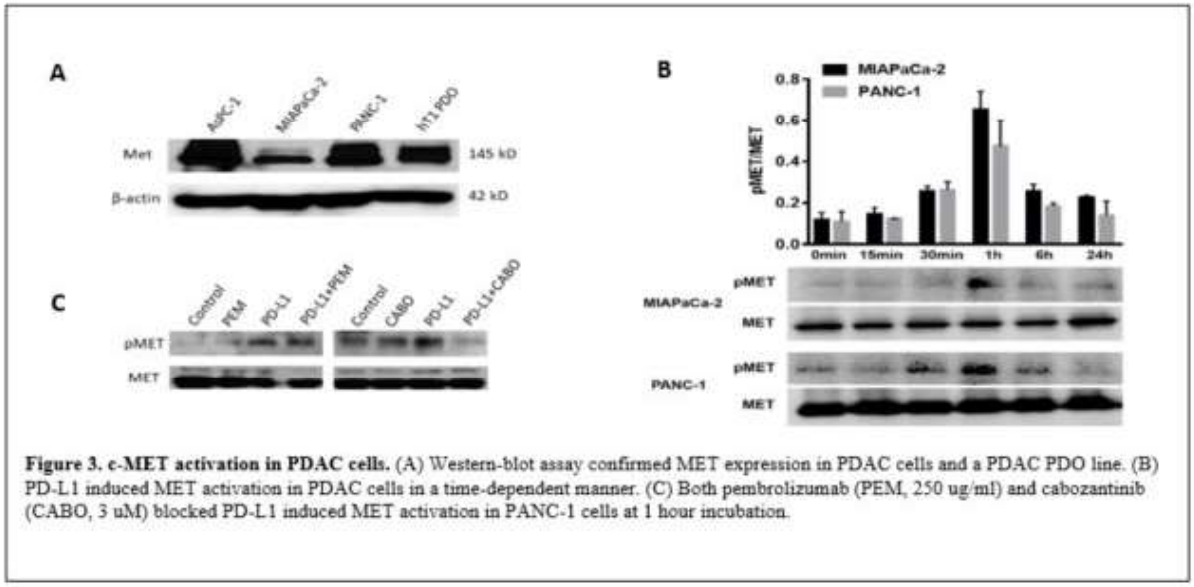


Figure 3. c-MET activation in PDAC cells. (A) Western-blot assay confirmed MET expression in PDAC cells and a PDAC PDO line. (B) PD-L1 induced MET activation in PDAC cells in a time-dependent manner. (C) Both pembrolizumab (PEM, 250 ug/ml) and cabozantinib (CABO, 3 uM) blocked PD-L1 induced MET activation in PANC-1 cells at 1 hour incubation.

2.5 Correlative Studies Background

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies, including novel combinations with anti-MET, is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response and resistance to cancer immunotherapy and other treatments administered, as well as determinants of adverse events (AEs) in the course of our clinical studies. These efforts may identify novel predictive or disease progression biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs.

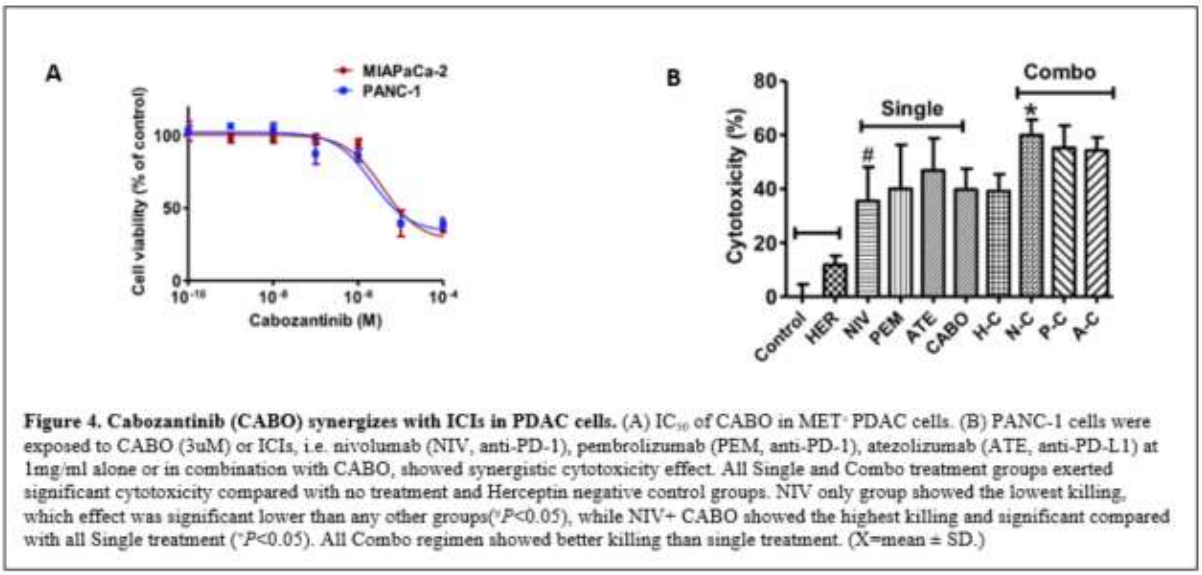


Figure 4. Cabozantinib (CABO) synergizes with ICIs in PDAC cells. (A) IC_{50} of CABO in MET+ PDAC cells. (B) PANC-1 cells were exposed to CABO (3uM) or ICIs, i.e. nivolumab (NIV, anti-PD-1), pembrolizumab (PEM, anti-PD-1), atezolizumab (ATE, anti-PD-L1) at 1mg/ml alone or in combination with CABO, showed synergistic cytotoxicity effect. All Single and Combo treatment groups exerted significant cytotoxicity compared with no treatment and Herceptin negative control groups. NIV only group showed the lowest killing, which effect was significant lower than any other groups(*P<0.05), while NIV+ CABO showed the highest killing and significant compared with all Single treatment (*P<0.05). All Combo regimen showed better killing than single treatment. (X=mean ± SD.)

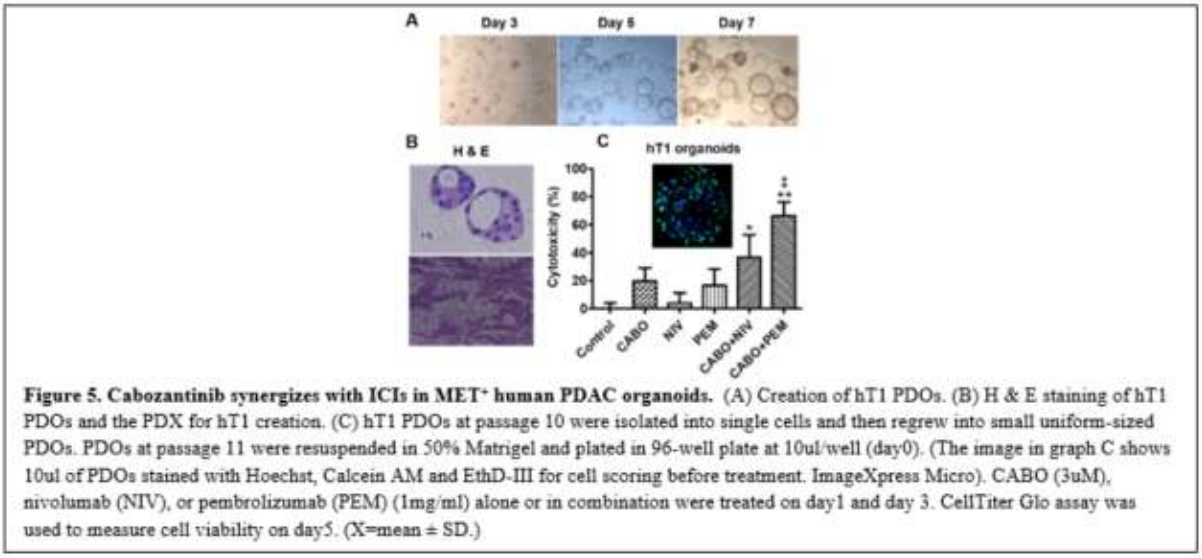


Figure 5. Cabozantinib synergizes with ICIs in MET+ human PDAC organoids. (A) Creation of hT1 PDOs. (B) H & E staining of hT1 PDOs and the PDX for hT1 creation. (C) hT1 PDOs at passage 10 were isolated into single cells and then regrew into small uniform-sized PDOs. PDOs at passage 11 were resuspended in 50% Matrigel and plated in 96-well plate at 10ul/well (day0). (The image in graph C shows 10ul of PDOs stained with Hoechst, Calcein AM and EthD-III for cell scoring before treatment. ImageXpress Micro). CABO (3uM), nivolumab (NIV), or pembrolizumab (PEM) (1mg/ml) alone or in combination were treated on day1 and day 3. CellTiter Glo assay was used to measure cell viability on day5. (X=mean ± SD.)

To accomplish these goals, we will examine plasma exosomal lipids and utilize patient-derived organoids (PDOs). Exosomes are extracellular vesicles released from cells that play a role in

intercellular signaling and transport of proteins, lipids, and nucleic acids. Exosomes are released from numerous cells in the body and have been detected in blood, bile, urine, cerebrospinal fluid, and tissues. Cancer cells produce elevated concentrations of exosomes compared to normal cells (Muralidharan-Chari et al, 2010). Cancer-derived exosomes interact with the tumor microenvironment and impact cancer proliferation, metastasis, immune evasion (Muralidharan-Chari et al 2010; Arscott et al, 2011; Costa-Silva et al, 2015; Gesierich et al, 2006; Upadhrasta et al, 2019; Zech et al, 2012) and drug resistance (Safaei et al, 2005; Yu et al, 2015). Our previous work revealed distinct lipid profiles in plasma exosomes from pancreatic cancer patients compared to healthy volunteers, thus highlighting the potential to use blood-based exosomal lipids as a biomarker for pancreatic cancer. Our group profiled exosomal lipids from 60 pancreatic cancer patients and 38 healthy volunteers. Our data showed that the exosomal lipid composition of pancreatic cancers was distinct from matched benign pancreatic tissues **(Fig. 6A)** and discriminated cancer from healthy controls **(Figs. 6B and 6C)**. By using advanced multivariate statistical approaches to analyze plasma exosomal lipid profiles of different cohorts, we observed a high sensitivity and specificity to detect pancreatic cancer with a set of 20 lipid features **(Figs. 7 and 8)**. These results demonstrated the potential for liquid biopsies to harbor exosomal lipids that are pancreatic cancer biomarkers that can be utilized to monitor responses to clinical therapies.

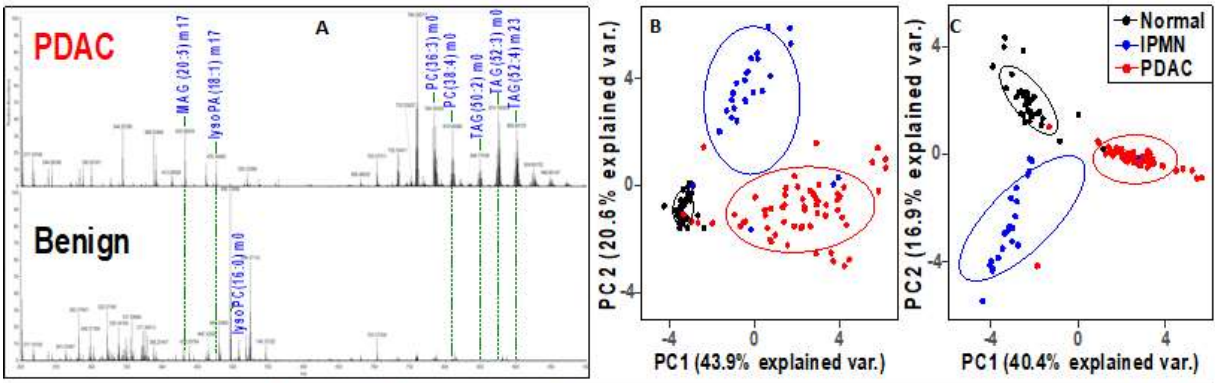


Figure 6. Lipid profiles are distinct for PDAC versus paired benign tissues while plasma exosomal lipid profiles clearly separate PDAC, precursor lesion (IPMN), and healthy donors. Tissue (**A**) and plasma exosomal lipids (**B**, **C**) were analyzed by Di-nESI-UHR-FTMS. Lipid species in **A** were assigned based on accurate mass and MS^2 fragmentation patterns using Thermo Lipid Search software. Principal component analysis (PCA) was performed on the exosomal lipids assigned by in-house software PREMISE without (**B**) or with individual ion intensities normalized to the summed ion intensity of lipids present in 30% of all samples (**C**). There was clear separation among 60 PDAC (•), 27 IPMN (•), and 38 healthy donors (•) (**B**, **C**) and the separation was improved with data normalization (**C**) with AUC ≈ 0.95-0.97.

PDOs are three-dimensional *in vitro* models used to study the biology of human cancers and their interactions with the cancer microenvironment. They function as miniature organs with cells that resemble the epithelium of origin by maintaining innate tissue cytoarchitecture, giving rise to distinct cell lineages, and undergoing self-renewal. Importantly, organoids possess all the genetic alterations present in the primary cancer tissues, making them precise genomic models of human cancers and have tremendous potential for predicting *in vivo* drug sensitivity (Boj et al, 2015; Gao et al, 2019; Tiriac et al, 2018). In prior studies, we observed that the results of drug testing in PDOs exactly mirrored the results from patient derived tumor xenografts, which is considered the gold standard cancer model. Since PDOs can be developed and drug tested rapidly, we propose to utilize this model to predict response to the proposed combination therapy. We will also determine if PDO prediction of therapy corresponds to data gathered from plasma exosome analysis.

To carry out these investigations, we will collect liquid biopsies from all patients prior to initiation of therapy and once monthly to determine if we can correlate clinical response to exosomal lipid levels. Methods for this analysis will follow prior investigations (Fan et al, 2018; Lane et al, 2009).

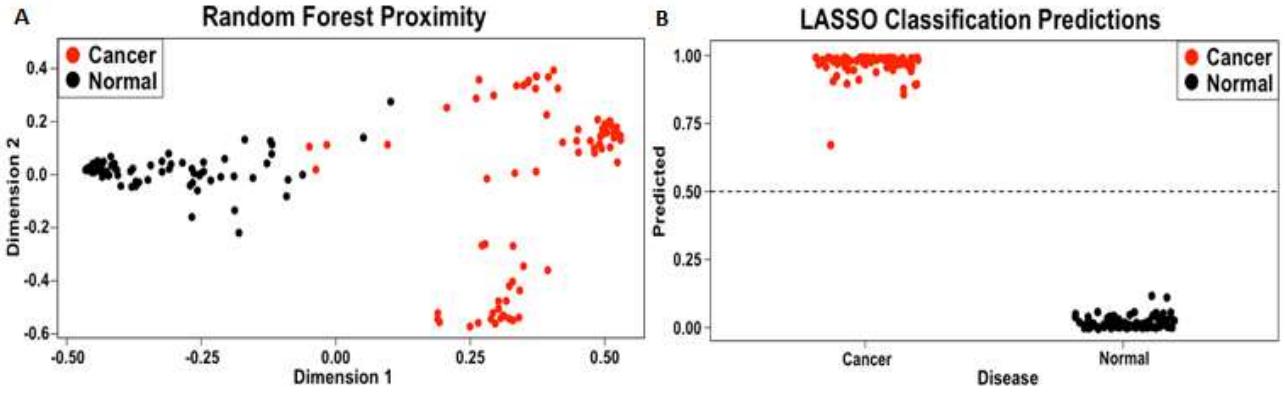
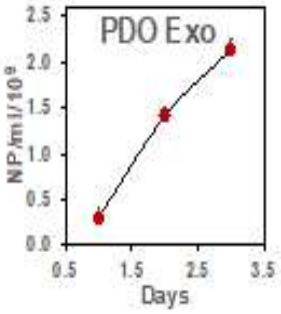


Figure 7. Supervised multivariate Random Forest and LASSO analyses of plasma exosomal lipid profiles show clear separation between pancreatic cancer and normal subjects. Both RandomForest (**A**) and LASSO (**B**) analyses were performed on 76 pancreatic cancer and 82 normal datasets. The study proposed here aims to identify plasma exosome lipid classifiers that discriminate PDAC from chronic pancreatitis, high risk individuals, and healthy controls.

Figure 8. Time course release of exosomes from PDAC PDOs. PDAC PDOs (n=3) were cultured in exosome-depleted media at 700,00 cells/50 µl droplet for 1 to 3 days and the nanoparticle (NP) or exosome concentrations in the culture media were analyzed by Nanosight. A time-dependent increase in the release of exosomes from PDAC PDO was evident.



We will collect tumor samples, when possible, for development of PDOs as previously described (Gao et al, 2018; Tiriac et al, 2018). These organoids will be used to test sensitivity to the combination of Cabozantinib and Pembrolizumab to predict clinical response.

2.6 Study Hypothesis

We hypothesize that Cabozantinib will synergize with Pembrolizumab to improve PFS in the 2nd line setting for patients with metastatic pancreatic cancer.

3. ELIGIBILITY

3.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

3.1.1 Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of pancreatic ductal adenocarcinoma, stage IV will be enrolled in this study.

3.1.2 Have measurable disease based on RECIST v1.1 (Response Evaluation Criteria in Solid Tumors). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

3.1.3 Evidence of progression or intolerance to previous standard of care pancreatic cancer systemic or locoregional therapies. Patients may have received prior radiation therapy and chemotherapy >4 weeks from start of treatment. Patients may not have been on prior clinical trial with investigational drugs for this cancer.

3.1.4 Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7-14 days prior to the first dose of study intervention. (see **Appendix A**).

3.1.5 Patients must have adequate organ function as defined below. Specimens must be collected within 14 days prior to the start of study intervention:

– absolute neutrophil count	≥1,500/μL
– platelets	≥100,000/μL
– hemoglobin	≥ 9.0 g/dL or ≥5.6 mmol/L; Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
– total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 x ULN
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × ULN (≤ 5 × ULN for participants with liver metastases)
– Alkaline phosphatase	≤ 3 × ULN
– International normalized ratio (INR) or prothrombin time (PT) and activated thrombo-plastin time (aPTT)	≤ 1.3 x ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants
– Serum Cr or measured or calculated creatinine clearance (GFR can be used in place of Cr or CrCl)	≤ 1.5 x ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec, using Cockcroft-Gault equation) for participants with Cr >1.5 x ULN
– Urine protein/creatinine ratio	UPCR ≤ 1 mg/mg (≤ 113.2 mg/mmol)

3.1.6 Patients must have a negative hepatitis screening test. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection

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

3.1.7 Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.

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

3.1.9 A male participant must agree to use a contraception during the treatment period and for 4 months after the last dose of study treatment and refrain from donating sperm during this period.

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section X:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile–vaginal intercourse or use a male condom during each episode of penile penetration.

3.1.10 A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

a. Not a woman of childbearing potential (WOBCP) or
b. A WOCBP who agrees to follow contraceptive guidance during the treatment period and for 4 months after the last dose of treatment.

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)
Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of

12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly.

Table 1. Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [a, b] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

3.1.11 The participant (or legally acceptable representative if applicable) has the ability to understand and the willingness to provide written informed consent for the trial.

3.1.12 Able to swallow oral medication

3.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

3.2.1 Chemotherapy or other locoregional anti-tumoral therapies performed within 28 days of study treatment initiation.

3.2.2 Has received palliative radiation therapy within 2 weeks or any other radiation therapy within 4 weeks of start of study intervention. Systemic treatment with radionuclides within 6 weeks before first dose of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

3.2.3 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1), unless AEs are clinically non-significant and/or stable on supportive therapy. Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

3.2.4 Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to allocation. Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible. If the participant received major surgery, the participant must have recovered adequately from the procedure and/or complications from the procedure and/or any complications from the surgery prior to starting study intervention.

3.2.5 Has known active CNS metastases or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

3.2.6 Has severe hypersensitivity (≥Grade 3) to pembrolizumab or cabozantinib and/or any of their excipients. History of allergic reactions attributed to monoclonal antibodies (mAb), compounds of similar chemical or biologic composition to Cabozantinib or Pembrolizumab.

3.2.7 Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

3.2.8 Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).

3.2.9 Prior treatment with Cabozantinib or other receptor for MET or dual MET/HGF monoclonal antibodies or MET/HGF tyrosine kinase inhibitors.

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

3.2.11 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), 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 of study treatment.
iii. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of study treatment.

3.2.12 Has a history of known additional malignancy that is progressing or has required active treatment within the past 3 years; or unless potentially curative treatment has been completed with no evidence of malignancy for 3 years. The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in-situ cancers (e.g., breast carcinoma).

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

Note: Inhaled, intranasal, intraarticular, and topical corticosteroids and mineralocorticoids are allowed. Transient short-term use of systemic corticosteroids for allergic conditions (e.g., contrast allergy) is also allowed. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.

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

3.2.15 Clinically significant cardiovascular disease, for example cerebrovascular accidents (less than 6 months, CVA) /stroke, myocardial infarction (also less than 6 months), unstable angina pectoris, New York Heart Association class 3 or 4 congestive heart failure, or serious cardiac arrhythmia requiring medication.

3.2.16 Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90mm Hg diastolic despite optimal antihypertensive treatment.

3.2.17 QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment.

Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility (i.e., if the average is ≤ 500ms the patient is eligible).

3.2.18 Concomitant anticoagulation with or plan to use oral anticoagulants (warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:

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

3.2.19 Pregnant, breastfeeding, and/or lactating women. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation will be excluded. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause).

3.2.20 Patients that are expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

3.2.21 Patients with uncontrolled intercurrent illness.

3.2.22 Patients with known psychiatric illness or substance abuse disorders or other social situations that would interfere with cooperation with the requirements of the trial.

3.2.23 Inability to swallow tablets.

3.2.24 Has had an allogenic tissue/solid organ transplant.

3.2.25 Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose of study treatment.

3.2.26 Cavitating pulmonary lesion(s) related to bacterial infections or pneumonia or known endotracheal or endobronchial disease manifestation. Note that cavitating pulmonary lesion(s) related to malignancy, with the exception of central lesions measuring ≥4 cm, are not excluded.

3.2.27 Lesions invading or encasing major blood vessels, specifically the abdominal aorta and inferior vena cava. Encasement of local vascular structure(s) is not excluded.

3.2.28 Other clinically significant disorders that would preclude safe study participation.
a. Serious non-healing wound/ulcer/bone fracture.
b. Uncompensated/symptomatic hypothyroidism

3.2.29 Moderate to severe hepatic impairment (Child-Pugh B or C).

3.2.30 Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention. Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

3.2.31 Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

3.2.32 Has an active infection requiring systemic therapy.

3.2.33 Has a known history of Human Immunodeficiency Virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

3.2.34 Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

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

3.2.36 Has a 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.

3.3 Inclusion of Women and Minorities

Women and members of minority groups and their subpopulations will be included.

4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES

4.1 Protocol Review and Monitoring Committee and Institutional Review Board

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee (PRMC). Additionally, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, and UK IRB.

4.2 Investigator and Research Associate Registration with MCC

All investigators must be qualified by education, training and experience to assume responsibility for the proper conduct of human subject research. Investigators are responsible for being able to provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation and training per institutional, state and federal guidelines. All investigators conducting MCC trials will register with the MCC Clinical Research Office and complete all requisite training and registrations per MCC SOPs.

4.2.1 Delegation of Tasks Log (DTL)

All MCC studies require a Delegation Task Log which is maintained by the MCC Regulatory Unit of the Clinical Research Office. The DTL for this study has training requirements as follows: In order to be added to the DTL for a given study, each staff member must have appropriate training to conduct assigned duties including but not limited to protocol-specific training. The DTL log will identify the protocol version on which each staff member was trained when being added to a study.

The Principal Investigator and Co-Investigator are responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Principal Investigator and Statistician have access to the study data at all times through OnCore. All decisions regarding dose modifications of HAI require consultation with the Principal Investigator.

4.3 Screening and Study Enrollment Guidelines

4.3.1 Overview

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be recruited from medical and surgical oncology clinics at the University of Kentucky Markey Cancer Center, with oversight by the Principal Investigator. The consenting professional will explain in detail the study to the patient and will review the informed consent with the patient (Section 4.4). Broadly, patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. A copy of the signed informed consent form is provided to the patient. Upon obtaining consent, study staff will register potentially eligible patients in the OnCore database. During the screening and enrollment process, registering individuals (study staff and PI) will be required to complete a protocol-specific Eligibility Checklist for each patient. The PI or treating physician signing the Eligibility Checklist is confirming whether or not the patient is eligible to enroll in the trial. Upon confirmation of eligibility, the patient will be enrolled into the study as participant (i.e., on-study date is entered in OnCore).

4.3.2 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.3.3 Screening and Enrollment Guidelines

Prior to any study-required tests, subjects must first provide written informed consent to participate in this study.

Pre-treatment evaluation and their corresponding timeframes **to screen for and verify eligibility** for study enrollment include the following:

- Medical History: within 4 weeks
- Physical Exam, Vitals: within 2 weeks prior to treatment initiation
- ECG: within 4 weeks
- Imaging to confirm disease at baseline: scans must be within 8 weeks
- ECOG Performance Status: within 2 weeks
- CBC w/ diff, platelets: within 2 weeks
- CMP (Alk phos, total bilirubin, AST, ALT, and albumin): within 2 weeks
- Urine protein/creatinine ratio (UPCR): within 2 weeks
- Urine/serum pregnancy test: within 4 weeks
- TSH: at baseline
- Viral serologies (hepatitis, HIV): these will be checked to assess current or past infection and viral load as indicated

4.4 Eligibility Confirmation and Enrollment

The following information should be reviewed by the Clinical Research Nurse (CRN) / Clinical Research Associate (CRA) with the study physician per MCC SOPs to confirm eligibility:

- Copy of required laboratory tests
- Pathology reports and Imaging reports
- Signed patient consent form
- HIPAA authorization form
- Physician dictations and Referring physician records (as available)
- Eligibility Checklist

Once eligibility is confirmed, the CRN/CRA will complete subject enrollment to the study in the OnCore database. To complete the enrollment process, the CRN/CRA will complete the OnCore on-study form, which comprises the following:

- Assignment of a patient study number
- diagnosis
- date of diagnosis
- histology
- entry of the On-Study date

Patients will be instructed to complete medication logs for Cabozantinib (“pill diaries”) and return the logs on clinic visits for review by the study team. See **Appendix B** for a sample Cabozantinib Medication Log.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Patient-derived organoids and exosomal lipids will be developed and tested to predict response to Cabozantinib and Pembrolizumab. To participate in this study's correlatives, enrolled trial participants will be asked to sign a separate consent in order for collection of blood/tumor tissue underlying analyses of exploratory endpoints (i.e., patient-derived organoids and exosomal lipids). Participation in the correlatives component is optional.

5.1 Summary for Specimen Collection

Specimen	
Archival Tumor Tissue (optional, if available)	
Archival Tumor Tissue to develop patient-derived organoids: Prospective biopsies are not required. If pancreatic cancer tissues from the patients enrolled on this clinical trial are available from prior biopsy and prior storage in Dr. Kim's biobank, they will be used to develop patient-derived organoids.*	
Pre-treatment Baseline (optional blood draw)	
Optional Blood Draw for Exosomal Lipids: 10 cc blood in lavender-top tube with EDTA. *	Send specimens to Dr. Teresa Fan lab
Once Monthly during the 6-month study period (optional blood draws)	
Optional Blood Draws for Exosomal Lipids: 10 cc blood in lavender-top tube with EDTA. * Cycle 2 visit Cycle 3 visit Cycle 4 visit Cycle 5 visit Cycle 6 visit Cycle 7 visit	Send specimens to Dr. Teresa Fan lab
*The samples for correlatives analyses will be collected via another protocol for biospecimen sample collection. Thus, patients enrolled on this clinical trial will be asked to sign a separate consent form for collection of blood and access to archival tumor tissue.	

5.2 Specimen Collection and Processing

As noted above, patients enrolled on this clincal trial will also be asked to sign a separate biospecimen consent, allowing collection of blood and access to archival tumor tissue (if available) that underlies the correlative studies of this trial. **Appendix C** describes procedures for establishing tumor organoid cultures from human pancreatic cancer specimens. **Appendix D** describes procedures for lipid exosomal analysis from plasma samples.

6. TREATMENT PLAN

6.1 Pembrolizumab/Cabozantinib Administration

Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1.1 First Dose of the Combination Therapy

The first doses of Cabozantinib and Pembrolizumab (C1D1) **will be administered at the clinic**; Pembrolizumab is to be administered first. After the completion of IV administration of the first dose of Pembrolizumab in the clinic, the subject will wait for at least 1 hour before taking Cabozantinib. If the subject develops an infusion reaction, the oral administration of Cabozantinib will be delayed or interrupted until the subject has recovered and the investigator believes that it is safe to administer Cabozantinib.

The subject will be fasted (with the exception of water) for at least 2 hours before receiving the initial dose of Cabozantinib in the clinic. The subject will receive the oral dose of Cabozantinib with a minimum of 8 oz. (240 mL) of water in the clinic and then the subject will continue to fast for 1 hour while under in-clinic observation to monitor for potential AEs.

6.1.2 Subsequent Daily Doses of Cabozantinib

Following the first dose of Cabozantinib, the subject should take subsequent Cabozantinib doses outside the clinic at approximately the same time every day, preferentially before going to bed, and should adhere to the fasting requirements described in this section. Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose. After the 2-hour fast and before going to bed, subjects are to take Cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose. If the subject's schedule requires taking Cabozantinib during the day, the subject is to be instructed to follow the same fasting recommendations.

6.1.3 Treatment Regimen

Table 2. Overview of Cabozantinib and Pembrolizumab Combination

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Pembrolizumab (MK-3475)	N/A	200 mg	IV infusion	Day 1, Q3 weeks	Q3 weeks
Cabozantinib (XL184)	1 hour before or 2 hours after meal; take dose with 8oz water (minimum). Swallow tablets (do not crush or chew). Avoid grapefruit and Seville oranges during treatment.	40 mg	Oral	Daily	

Notes:

Cabozantinib:
Subjects are to be instructed to not make up vomited doses and to maintain the planned dosing schedule. Subjects are not to make up for missed doses if more than 12 hours have elapsed after the time the subject would usually take Cabozantinib. In the event of missed doses, subjects are not to take 2 doses to make up for the one the subject missed.

Participants will be provided a daily dosing diary with instructions to record Cabozantinib, in accordance with the SOP on compliance with oral medications per Markey Cancer Center Quality Assurance Office.

- The patient will be requested to maintain a medication diary of each dose of medication. The diary will be distributed on C1D1 and collected at the beginning of Cycle 2, etc.
- The medication diary will be returned to clinic staff at the end of each 21-day course.
- The daily diary is not a CRF. The diary will serve as source documentation and be maintained with other subject clinical source documents.
- Study staff should carefully review the diary with the subject and to ensure it is complete and accurate before transcription to the subject's CRFs.

Pembrolizumab Infusion Requirements and Guidance	
<u>First</u> Infusion	**Subsequent Infusions:**
• No premedication is permitted. • Vital signs (blood pressure, respiratory rate, pulse, and temperature) should be recorded within 60 min prior to the infusion. • Pembrolizumab should be infused over 30 min (-5 min/+10 min). • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 min (± 5 min for all time points) during the infusion and at 30 (± 10) min after the infusion. • Subjects should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their physician	• If the subject experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 min prior to the infusion. • Pembrolizumab should be infused over 30 (± 15) min if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) min if the subject experienced an infusion-related reaction with the previous infusion. • If the subject experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 5) min after the infusion.

6.2 General Concomitant Medication and Supportive Care Guidelines

The chemotherapy pharmacist will review all medications (concurrent use of other all other drugs, over the counter medications or alternative therapies) for interactions at the start of therapy and new medications will be reviewed if started. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

<u>Rescue Medications & Supportive Care</u>

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in the protocol. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures, unless the participant has withdrawn from the study.

Participants may discontinue study intervention at any time for any reason or be discontinued 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 or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsors.
- Confirmed radiographic disease progression
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The participant is lost to follow-up
- Completion of 17 treatments (approximately 1 year) with the combination of cabozantinib and pembrolizumab or an additional 18 treatments with pembrolizumab monotherapy (total 35 treatments)

  Note: The number of treatments is calculated starting with the first dose.

  Note: Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of cabozantinib beyond the date when the initial CR was declared.
- Administrative reasons

Participant withdrawal From Study
A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study as well as specific details regarding withdrawal from future biomedical research are outlined in this protocol.

6.3 Compliance

Subject compliance with outpatient study treatment will be assessed using drug dispensing and return records, progress notes about dose reductions/interruptions, subject interview, and the subject daily diary (Cabozantinib). These data will not be directly recorded in the CRF; rather, the CRF will capture intervals of constant dose and reasons for changes in dose level (e.g., dose level changes, periods where no dose was taken, and the reason for a dose level change).

6.4 Duration of Therapy

In the absence of treatment delays due to adverse events, the combination Cabozantinib + Pembrolizumab therapy may continue for up to 17 cycles in total (1 year of treatment); and up to 35 cycles (2 years of treatment) with pembrolizumab monotherapy. Pembrolizumab treatment is administered Q3W which is defined as 1 cycle. Treatment will continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

Note: Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of cabozantinib beyond the date when the initial CR was declared.

6.5 Duration of Follow-Up

Safety:
Patients will be followed for safety of the Cabozantinib/Pembrolizumab combination therapy for 100-days after the last dose of Pembrolizumab (or the combination).
Patients removed from the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Survival:
Patients will be followed for disease progression and survival status up to 1 year post-therapy initiation or until death, whichever occurs first.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Cabozantinib (investigational) and Pembrolizumab (commercial) can be found in Section 10.1.

7.1 Drug Ordering and Accountability

7.1.1 *Procurement of medications:*
Prescriptions for medications will be written by the site PI, treating physician, preferably the medical oncologist, using study-approved standardized Markey Cancer Center order sets. The clinical research pharmacist of the MCC-CRO will review and approve these orders per published MCC polices. Drug accountability will be maintained on a Drug Accountability Report Form (DARF).

7.1.2 *Storage & Drug Accountability:*
The clinical research pharmacist at MCC-CRO will ensure that all study drug is stored in a secured, limited access storage area, under recommended storage conditions in accordance with applicable labeling and regulatory requirements and as provided by the separate study drug accountability manual. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics. Adequate records documenting receipts, use, return, loss, or other disposition of study provided drugs must be kept. Drug accountability forms will be used, per institutional policies. Unless otherwise authorized by the co-sponsors, at the end of the clinical trial all drug supplies unallocated or unused by MCC or study patients must be returned in accordance with sponsors' instructions.

7.2 Cabozantinib

7.2.1 Product Description and Administration
Exelixis (one of the two co-sponsors) will provide adequate supplies of Cabozantinib, which will be supplied as 40-mg yellow film-coated tablets and also as 20-mg yellow film-coated tablets. The components of the tablets are listed below.

> 40 mg Cabozantinib tablets are yellow film-coated, oval shaped with no score, and debossed with "XL" on one side and "60" on the other side.
>
> 20 mg CABOMETYX tablets are yellow film-coated, round with no score, and debossed with "XL" on one side and "20" on the other side.

Table 3. Cabozantinib Tablet Components and Composition		
Ingredient	**Function**	**% w/w[a]**
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00
a weight fraction, expressed in percentage; HPMC, Hydroxypropyl methylcellulose		

Preparation, Storage and Stability
Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

Administration
Refer to the treatment section for specific administration instructions. Oral: 40 mg once daily, continue as long as benefiting clinically or until unacceptable toxicity (Choueiri 2021); do not exceed 60 mg daily. Administer on an empty stomach (1 hour before or 2 hours after eating).

Note: The prescribing information (for Cometriq) describes when to give food with respect to Cabozantinib; no food should be consumed for at least 2 hours before or for at least 1 hour after the Cabozantinib dose. Swallow whole; do not crush tablets. Do not substitute Cabozantinib tablets.

7.2.2 Adverse Events from Cabozantinib monotherapy
Consult the package insert and investigator brochure for the most current and complete information.

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

Other **medically important** but less frequent AEs including arterial thrombotic AEs (e.g., TIA, and MI) and venous thrombotic AEs (e.g., DVT and PE), severe hemorrhagic events, proteinuria, wound-healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

Adverse events associated with **laboratory abnormalities** experienced by ≥ 5% of subjects treated with Cabozantinib in descending order of frequency were anemia, AST increased, ALT increased,

hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

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

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.

Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with Cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage et al, 2016) are present. Discontinue Cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

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

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

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions.

Non-gastrointestinal Fistula

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

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

Hemorrhage

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

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

Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and PE have been observed in clinical studies with Cabozantinib, including fatal events. Subjects who develop a PE and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with Cabozantinib may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from Cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed except under the following circumstances:

Allowed anticoagulants are the following:

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

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.

Hypertension

Appendix D provides treatment guidelines for hypertension deemed related to Cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in

a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Cabozantinib should be discontinued in subjects with hypertensive emergency.

Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with Cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

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

Skin and Subcutaneous Tissue Disorders

Wound healing and surgery:

Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 3 weeks prior to elective surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until complete wound healing.

Palmar-plantar erythrodysesthesia (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with Cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.
Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral.

Osteonecrosis

Osteonecrosis has been reported in subjects treated with Cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain

or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

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

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.

Proteinuria

Proteinuria has been reported with Cabozantinib. Proteinuria should be monitored by measuring UPCR Appendix D provides treatment guidelines for proteinuria deemed related to Cabozantinib.

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

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.

Reversible Posterior Leukoencephalopathy Syndrome (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.

Blood and Lymphatic System Disorders

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of Cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

Corrected QT Prolongation

The effect of orally administered Cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with medullary thyroid cancer (MTC). A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating Cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No Cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (approximately 5000 subjects exposed to Cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

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

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

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

- Interrupt Cabozantinib treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

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

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

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

Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g., after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.

Fatigue

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

Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with Cabozantinib, and serum electrolyte levels should be monitored frequently while receiving Cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or IV replacement.

Endocrine Disorders

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

Hepatocellular Toxicity

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with Cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other causes (e.g., cancer related, infection) should be evaluated.

Management guidelines for hepatotoxicity related to Cabozantinib treatment are in **Appendix E**. More frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize to clinically acceptable levels (e.g., baseline grade or lower). If hepatic toxicity resolved during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment.

7.2.3 Management of Adverse Reactions from Cabozantinib

Withhold CABOZANTINIB for NCI CTCAE Grade 4 adverse reactions, and for Grade 3 or intolerable Grade 2 adverse reactions that cannot be managed with a dose reduction or supportive care.

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

- If previously receiving 60 mg daily dose, resume treatment at 40 mg daily
- If previously receiving 40 mg daily dose, resume treatment at 20 mg daily
- If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue CABOZANTINIB

Permanently discontinue CABOZANTINIB for any of the following:

- development of unmanageable fistula or GI perforation
- severe hemorrhage
- arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- hypertensive crisis or severe hypertension despite optimal medical management
- nephrotic syndrome
- reversible posterior leukoencephalopathy syndrome

In Patients Concurrently Taking a Strong CYP3A4 Inhibitor: Reduce the daily CABOZANTINIB dose by 20 mg (for example, from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor

In Patients Concurrently Taking a Strong CYP3A4 Inducer: Increase the daily CABOZANTINIB dose by 20 mg (for example, from 40 mg to 60 mg daily or from 20 mg to 40 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of CABOZANTINIB should not exceed 80 mg.
In Patients with Hepatic Impairment: Reduce the starting dose of CABOZANTINIB to 20 mg once daily in patients with mild or moderate hepatic impairment. CABOZANTINIB is not recommended for use in patients with severe hepatic impairment.

Nursing Guidelines
Monitor vital signs prior to infusion, then every 15 minutes until 1 hour after infusion on first dose.

All patients with a history of infusion reactions to this immunotherapy should be monitored every 15 minutes until 1 hour after the end of the infusion.

7.3 Pembrolizumab

Consult the package insert and investigator brochure for the most current and complete information.

7.3.1 Product description:
The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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

Pembrolizumab will be provided by Merck as summarized in the table below.

Table 4. Product Description

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

Packaging and Labeling Information
Supplies will be labeled in accordance with regulatory requirements.

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

Storage and Handling Requirements
Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Returns and Reconciliation
The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7.3.2 Dose modification and toxicity management for immune-related Adverse Events associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, 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, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab/combination treatment and administer corticosteroids.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event [to the combination, to cabozantinib alone, or to pembrolizumab alone] for adverse events, both interventions must be held according to the criteria in section 8.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study as described in Table 19.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in [Table 19], the combination of cabozantinib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to cabozantinibi alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

7.3.3 Management of Adverse Reactions to Pembrolizumab dose holds or discontinuation

Dose modification (Section 8) and toxicity management guidelines for irAEs in **Appendix F**.

8. DOSING DELAYS/DOSE MODIFICATIONS

Study participants will be monitored for AEs from the time of signing consent through 100-days after the date of the decision to permanently discontinue all study treatment (i.e., last dose). Participants will be instructed to notify their physician immediately for any occurring AE.

The following should be taken into consideration in decisions regarding dose modifications (reductions and/or delays) for treatment-related side effects.

Cabozantinib and Pembrolizumab have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs that can be clearly attributed to Cabozantinib or Pembrolizumab, independent dose modification for either agent is allowed.

- Examples of VEGFR TKI associated AEs caused by Cabozantinib are hypertension and hand-foot syndrome.
- Examples of irAEs and common AEs caused by Pembrolizumab are fatigue,

musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

- Examples of overlapping AEs are diarrhea and elevations in liver function tests.

Table 5. Dose Modifications.

Dose Level	Cabozantinib Dose	Pembrolizumab Dose
0 (starting dose)	40 mg, oral, qd	200mg, IV, Q3weeks
-1	20 mg, oral, qd	200mg, IV, Q3weeks
-2	20 mg, oral, qod	200mg, IV, Q3weeks
-3	Discontinue Cabo	200mg, IV, Q3weeks

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.1 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsors (Exelixis & Merck), and the participant.

Acceptable Concomitant Medications

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

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

All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered 30 days after the last dose of trial intervention are to be recorded.

8.2 Prohibited or Restricted Medications or Therapy

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive Cabozantinib until they have permanently discontinued Cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval.
- Anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel) are prohibited.
- Co-administration of Cabozantinib with strong inhibitors of the CYP3A4 family may increase Cabozantinib concentrations and should be avoided. See **Appendix G**.
    - Strong CYP3A4 inhibitors: if possible, avoid concomitant use with Cabozantinib.
      Examples of strong CYP3A4 inhibitors include: Boceprevir, clarithromycin, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, atazanavir, telaprevir, telithromycin, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir/ritonavir, and voriconazole.
    - Grapefruit, grapefruit juice, star fruit and Seville oranges may also increase plasma concentrations of Cabozantinib and should also be avoided.
    - Other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to Cabozantinib.
    - Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.
    - When concomitant use of strong CYP3A4 inhibitors *cannot be avoided*, reduce Cabozantinib dose by 20 mg.
    - Resume Cabozantinib at the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

- Chronic co-administration of Cabozantinib with strong inducers of the CYP3A4 may significantly decrease Cabo concentrations and should be avoided. See Appendix F.
    - Strong CYP3A4 inducers: if possible, avoid concomitant use with Cabozantinib.
      Examples of strong CYP3A4 inducers include: Rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital and St. John's wort.
    - Other drugs that induce CYP3A4 should be used with caution as these drugs have the potential to decrease exposure (AUC) to Cabozantinib.
    - Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended for subjects receiving Cabozantinib.
    - Caution must be used with 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 exposure to Cabozantinib.
    - When concomitant use of strong CYP3A4 inducers *cannot be avoided*, increase Cabozantinib dose by 20 mg.
    - Resume Cabozantinib at the dose used prior to initiating the strong CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer.
        - Do not exceed daily dose of 60 mg (Cabozantinib).

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than cabozantinib or pembrolizumab
- Radiation therapy: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not 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 Sponsors.

Participants 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. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsors (Exelixis & Merck), and the participant.

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

A single arm, Phase II trial will be performed using combination Cabozantinib and Pembrolizumab in patients with refractory pancreatic cancer. The primary study endpoint is PFS compared to historical PFS.

9.2 Sample Size/Accrual Rate

The historical median PFS for 2nd line metastatic pancreatic cancer will be assumed to be 2.0 months. We hypothesize an improvement in PFS to 4.0 months for this combination regimen.

A sample of 21 evaluable patients will provide 80% power to detect this hypothesized improvement in PFS with 80% power based on a one-sided log-rank test with 5% alpha and an

exponential distribution with an interim analysis plan (Section 9.6). Patient accrual is projected for 24 months with an estimated enrollment of 1 patient per month and 6 months of follow-up after the last patient is enrolled in the trial. Assuming a 5% unevaluable or drop-out rate, a sample of 23 patients will be enrolled in the Phase II trial.

9.3 Stratification Factors

None.

9.4 Analysis of Primary Endpoint

PFS will be estimated using the Kaplan-Meier curve and median PFS and confidence interval will be calculated. The one sample log-rank test will be employed to test improvement in PFS with the combination regimen. Exploratory analysis using the Cox regression model to assess PFS adjusted for a few key clinical parameters will be performed. An intent-to-treat analysis, wherein all patients who received study drug, will be the primary analysis of the PFS outcome.

Given that the timing of radiology scans is every Q8 weeks (+/- 1-2 weeks) or scans as clinically indicated, we will consider the analysis of PFS as interval censored data. The SAS ICLIFETEST will be used for nonparametric survival analysis of interval-censored data while SAS LIFEREG can deal with parametric survival model with both interval and right censored data. The R package for interval censored data (icenReg) which can do nonparametric, parametric and semiparametric Cox models will also be implemented.

9.5 Secondary Endpoints

All patients who received study drugs will be included in the safety analysis. The maximum grade of toxicity for each AE category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all serious (≥ grade 3) toxicity events on a patient-by-patient basis. Frequency and incidence tables of toxicity and AEs will be generated.

Other time-to-event endpoints including OS will be estimated using survival analysis methods. Overall response rate and benefit response rate will be estimated along with the exact 95% binomial confidence intervals.

Bioinformatics methods for data processing and data analysis pipelines will be applied and exploratory comparisons of exosomal lipid and organoid cytotoxicity profiles with response and clinical outcomes will be performed using two sample t-test or linear models with control for false discovery rate (FDR).

9.6 Interim Analysis

Interim analysis will be performed based on an optimal two-stage design for Phase II survival trials. Specifically, an exponential distribution with an exact variance estimate of the one-sample log-rank test (OSLT) will be used for the two-stage design (Wu, 2015). Using the R function Optimal.rKJ, this two-stage design assuming an exponential distribution will enroll 14 patients at the first stage. At the time of interim analysis, each patient is followed for an event (disease progression or death) or is censored. If the first stage test statistic $Z1 < 0.088$, we stop the trial for futility. Otherwise the trial continues to the second stage until a total of 21 evaluable patients is enrolled on the study. The final analysis will be conducted when all patients have been enrolled.

If the second stage test statistic $Z < 1.632$, we don't reject the null hypothesis and conclude no efficacy of the treatment. If $Z \geq 1.632$, we conclude that the treatment is promising.

9.7 Reporting and Exclusions

9.7.1 Evaluation of Toxicity

All patients who received study drug will be evaluable for toxicity and included in the safety analysis from the time of their first treatment with Cabozantinib and Pembrolizumab combination treatment.

9.7.2 Evaluation of Response

An intent-to-treat analysis will be employed for assessment of clinical endpoints. All patients who met the eligibility criteria and received the study medication are included in the primary analysis. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of primary endpoint and the response rate.

9.8 Clinical Trial Registration with NIH

All clinical treatment trials have to be registered into clinicaltrials.gov before opening to accrual and trial results have to be published. The MCC-CRO Regulatory unit (mccreg@uky.edu) supports investigators in completing registration and renewal of their trials to NIH system in conjunction with a representative from UKHC. Results of this trial will be released on Clinicaltrials.gov within 12 months after follow-up is completed (of final patient accrued). If the trial is stopped early, data will be posted within six months of the study's termination.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports are listed below.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

10.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html)
  All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. CTCAE version 5.0 can be downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

Adverse Event (AE) definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Merck product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by Merck for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Definition of SAE
If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

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

a. Results in death
b. Is life-threatening

   The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

   Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the participant's medical history.
d. Results in persistent or significant disability/incapacity

   The term disability means a substantial disruption of a person's ability to conduct normal life functions.

   This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

   In offspring of participant taking the product regardless of time to diagnosis.
f. Other important medical events

   Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

   Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose of pembrolizumab

AE and SAE recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

There may be instances when copies of medical records for certain cases are requested by the Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Merck.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

   Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

   Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

   Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

   Grade 4: Life threatening consequences; urgent intervention indicated.

   Grade 5: Death related to AE.

Assessment of causality

1. Did Merck product cause the AE?
2. The determination of the likelihood that Merck product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
3. The following components are to be used to assess the relationship between Merck's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the AE:

   Exposure: Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

   Time Course: Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

   Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

   Dechallenge: Was Merck product discontinued or dose/exposure/frequency reduced?

   If yes, did the AE resolve or improve?

   If yes, this is a positive dechallenge.

   If no, this is a negative dechallenge.

   (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; (3) the study is a single-dose drug study; or (4) Merck product(s) is/are only used 1 time.)

   Rechallenge: Was the participant re-exposed to Merck product in this study?

   If yes, did the AE recur or worsen?

   If yes, this is a positive rechallenge.

   If no, this is a negative rechallenge.

   (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Merck product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF RE-EXPOSURE TO MERCK'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).

   • Yes, there is a reasonable possibility of Merck product relationship:

   • There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.

   • No, there is not a reasonable possibility of Merck product relationship:

   • Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)
7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Merck. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Merck.
9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to Merck within 2 business days but no longer than 3 calendar days of receipt of the information.

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Merck
SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

Adverse events (AEs), SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

The following list of AEs (Section 10.1) and the characteristics of an observed AE will determine whether the event requires expedited reporting to Overall PI and DSMC via the OnCore **in addition** to routine reporting.

Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information
All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify Merck.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in the Table below.

Table 6. Reportable safety events.

Type of Event	**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and

overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome.

Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to Merck.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to Merck.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be 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 adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

10.2 MCC Expedited Adverse Event Reporting Guidelines

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy, as specified in the table in below. Use the MCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

10.2.1 MCC Required forms and reporting structure

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
IIT by MCC investigator sponsored by industry	• Grade 3 –Unexpected AE PLUS Possibly, Probably or Definitely Related • ALL Grade 4 Unless expected AND listed in protocol as not requiring reporting. • ALL Grade 5 (fatal) Events	FDA: Suspected AE that is serious and Unanticipated (not listed in IDB or consent)	OnCore and DSMC reporting only	Voluntary Medwatch 3500 for Serious and unanticipated OnCore for all AEs, including SAEs	Per SOPs

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.2.2 Expedited Reporting guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy.

Table 10.3.2 -- MCC Reportable AEs

Attribution	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*

NOTES:
If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last Intervention/dose, the AE should be reported within <u>24 business hours</u> of learning of the event.

10.3 Expedited Reporting to External Agencies

The PI will comply with the policies of all external funding agencies (Exelixis, Merck) and the UK IRB regarding expedited reporting, as per the UK IRB's Mandated Reporting to External Agencies SOP C4.0150.

As soon as an Investigator becomes aware of an AE that meets the criteria for an SAE, the Investigator will document the SAE on an SAE Report Form or in an electronic database. SAEs, regardless of causal relationship, must be reported to Exelixis within one (1) business day of the Investigator's knowledge of the event by submitting a completed SAE report form. The reports must be emailed to **drugsafety@exelixis.com** or faxed to **650-837-7392** with the below:

- Required Information:
  - Identity of Investigator
  - Site name
  - Subject identifiers
  - Drug name and dosage
  - Event description
  - Event terms (i.e., as recorded in the electronic database)
  - Investigator's assessment of the relationship of the event to study treatment
  - The reason why the event is considered to be serious

- Recommended Information:
  - Medications or therapeutic measures used to treat the event
  - Action taken with the study treatment because of the event
  - Outcome/resolution of the event
  - Any additional SAE information

Note – Medical records should **not** be sent to Exelixis unless requested.

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

SAEs that must be recorded on an SAE Reporting form include the following:

- SAEs that occur after informed consent or study initiation and through 30 days after the date of the decision to permanently discontinue study treatment
- SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the date of the decision to permanently discontinue study treatment.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Exelixis.

When reporting SAEs, the following additional points will be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator will report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated, and the diagnosis amended when the etiology has been identified. If an autopsy was performed, the autopsy report should be provided.

10.4 Expedited Reporting to the Food and Drug Administration (FDA)

The PI, as study sponsor, will be responsible for all communications with the FDA. The PI will report to the FDA any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

10.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

10.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions with the exception of those listed in Section 10.4. **AEs reported expeditiously to the Overall PI and DSMC via OnCore must <u>also</u> be reported in routine study data submissions.**

10.7 Pregnancy

Pregnancy is considered an unanticipated event and pregnancy as well as its outcome must be documented and reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Any pregnancy occurring in a patient or patient's partner from the time of consent to approximately 4 months after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study

Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck.

10.8 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.9 Second Malignancy

A *second* malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted prior to start of protocol therapy as noted in the study calendar. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-enrollment	Planned Cabo/Pembro Treatment * *Cabozantinib daily concurrent w/ Pembrolizumab Q3 wks*			Safety *(100-days after final dose)*	1-year Post Treatment Initiation	Off - Study
Assessment:	**Screening**	**Cycle 1**	**Cycles 2 - 8**	***Cycles 9 - 17***			
Visit Windows	**Day -30 to -1**	**(± 3 days)**	**(± 3 days)**	***(± 7 days)***	**(+14 days)**	**(+14 days)**	**---**
Informed consent	X						
Demographics, medical history	≤ 28 days						
Physical exam	≤ 14 days	X / Day 1 (C1-C8)		X / Day 1 of odd cycle	X	X	
Weight	≤ 28 days	X / Day 1 (C1-C8)			X	X	
Height	≤ 28 days	X					
ECOG PS	≤ 14 days	X / Day 1 (C1-C8)		X / Day 1 of odd cycle	X	X	
Vital signs	≤ 14 days	X / Day 1 of every cycle			X	X	
12-lead ECG	≤ 4 weeks	As clinically indicated.		As clinically indicated	As clinically indicated	As clinically indicated	
CBC w/ diff, platelets	≤ 14 days	Day 1 all cycles. Record in the eCRF: ANC, plts, Hemoglobin			X	X	
CMP	≤ 14 days	Day 1 of every cycle / only record results for the following in the eCRF: alk phos, total bilirubin, AST, ALT, albumin			X	X	
Hepatitis screening	X						
PT/INR, aPTT	≤ 14 days						
Urinalysis	≤ 14 days	X/ Day 1 of cycles 1 - 8		As clinically indicated	As clinically indicated	As clinically indicated	
Urine chemistry (UPCR)	≤ 14 days	X	Q6 weeks at clinic visit	As clinically indicated	As clinically indicated	As clinically indicated	
Pregnancy test	≤ 28 days	X					
TSH	≤ 14 days	X	Q6 weeks at clinic visit				
CA19-9	≤ 14 days	X, optional	CA19-9 may be evaluated at physician discretion per institutional standards.				
Imaging: **CT/MRI C/A/P**	Within 8 weeks of treatment initiation	CT of the chest, abdomen, and pelvis or CT of the chest with MRI of the abdomen and pelvis will be performed in all subjects at screening and every 8 weeks (± 14 days) after first dose of Pembro/Cabo combination treatment for the first 6-months on-study or as clinically indicated. Upon completion of 6 months on study, these assessments will be performed every 12 weeks (± 7 days) up to 12-months post-treatment initiation. Tumor imaging will continue until either 12-months post-treatment initiation OR until radiographic disease progression per RECIST 1.1 as determined by the investigator. PR or CR per RECIST 1.1 at a given time point must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met.					

Correlative: Blood samples for Exosomal Lipids **(optional)**	See ** below. These 7 blood draws for Exosomal Lipids are optional, and will be collected via another biospecimen sample collection protocol. 10cc blood in lavender-top tube w/ EDTA will be collected at the following 7 timepoints: Pre-treatment baseline: i.e., predose Cycle 2 clinic visit Cycle 3 clinic visit Cycle 4 clinic visit Cycle 5 clinic visit Cycle 6 clinic visit Cycle 7 clinic visit collected once monthly for 6-months (i.e., at clinic visit during Cycles 2 – 7). The first blood draw is prior to Cycle 1; the second blood draw occurs immediately prior to Cycle 2 (i.e., blood is drawn on day 1 of each cycle, up to Cycle 7).						
Correlative: Archival Tumor **(optional)**	*** If archival tissue is available, tumor tissue will be obtained via another protocol for biospecimen sample collection for correlative, patient-derived organoids. Patients enrolled on this trial will have to sign a separate consent for utilization of archival tissue.						
Con Meds	X [1]	X [2]	X [2]	X [2]	X [2]	X [2]	
Adverse Events	≤ 28 days	X	X	X	X	X	
Pembrolizumab (IV infusion)		X, q3 weeks for 8 cycles.		*Could continue*			
Cabozantinib (oral med)		C1 Day 1 dose given in clinic to monitor safety. C1 D2-D21 doses are taken at home.	X, Daily dose taken at home C2-C8	*Could continue*			
		Cabozantinib dispensed to subjects every 3 weeks.					
Cabozantinib daily dosing diary		The patient will record the daily amount of Cabozantinib taken in an oral medication log from Cycles 1-8 (i.e., C1D1 to C8D21).					
Tumor Assessment to determine PFS and ORR		Imaging/scans will be assessed per RECIST and iRECIST and the results (PR, CR, etc.) will be noted in the eCRF to support interim analysis (initial 14 patients) and the final analysis if the trial is not stopped early for futility.					
Survival Status		Interim analysis will be conducted after the first 14 patients are enrolled and will be followed for an event (disease progression, death).		Survival Status will be ascertained until death or until 1-year post-treatment initiation.			
Early Discontinuation		X, (note reason for early DC of treatment **and/or** reason for removal from study participation)					
	Screening	**Cycle 1**	**Cycles 2 - 8**	**Cycles 9 - 17**	**Safety 100-Days after final dose**	**1-year post-treatment initiation**	**Off -Study**

FOOTNOTES to Study Calendar:

* Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of cabozantinib beyond the date when the initial CR was declared.

** **Exosomal lipids correlative**: Blood samples for exosomal lipids are optional, and will be obtained via another protocol for biospecimen sample collection. Patients enrolled on this trial will have to sign a separate consent for participation in the correlative studies. 10cc blood in lavender-top tube EDTA will be collected at pre-treatment and then, once monthly for 6-months (i.e., at the clinic visit for Cycles 2 – 7).

*** **Patient-derived organoids correlative**: Tumor tissue will be obtained via another protocol for collection of biospecimen samples. Patients enrolled on this trial will have to sign a separate consent for tissue collection (i.e., in order to participate in the correlative studies).

1: Con meds at screening: Record meds only if given within 28 days of treatment.

2: Con Meds after screening visit: CON meds should be recorded up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered 30 days after the last dose of trial intervention are to be recorded.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *8* weeks during the first 6-months, and thereafter, every 12 weeks up until 1-year post-treatment initiation or disease progression or death, whichever occurs first.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST, v1.1; Eisenhauer et al, 2009) and iRECIST guidelines (Seymour et al, 2017). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Pembrolizumab/Cabozantinib combination.

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

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

12.1.2 Disease Parameters

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

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are

present in the same patient, these are preferred for selection as target lesions.

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

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

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

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

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

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

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

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

12.1.4.3 Evaluation of Best Overall Response

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

12.1.5 Duration of Response

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

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

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. An intent-to-treat analysis, wherein all patients who received study drug, will be the primary analysis of the PFS outcome.

Table 8. Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/ Non-PD/ not evaluated	No	PR	
SD	Non-CR/ Non-PD/ not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

Table 9. Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

12.2 Antitumor Effect – Immune-Related RECIST (iRECIST) Criteria

12.2.1 Definitions

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment with Pembro/Cabo combination.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (RECIST version 1.1, Eisenhauer et al, 2009) proposed by the RECIST Committee as well as the modified iRECIST guidelines (Seymour et al, 2017). Investigators should note the different requirements for confirmatory scans as well as follow-up for the two criteria.

12.2.2 Image Receipt and Processing

Images will be reviewed by either a UK radiologist or sent to Dr. Jinha Park at The Radiology Experts, Inc. De-identified images without any patient identifiers will be submitted to Dr. Park at The Radiology Experts, Inc (central radiology) by express mail for assessment of treatment response. Submission can occur via upload of redacted images via compatible physical support (e.g., CD-ROM).
Dr. Park will provide RECIST and iRECIST measurements within 24-48 hours after receipt.

12.2.3 Site Performing Imaging Reads

De-identified images on physical support will be shipped from the University of Kentucky to:

Jinha Park, MD, PhD
5825 Lincoln Avenue, Suite D330
Buena Park, CA 90620

12.2.4 RECIST v1.1 Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed

to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

12.2.5 Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases (Eisenhauer et al, 2009) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 10. Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
Target lesions ± non-target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/ non-PD	No	PR	Normalization of tumor markers, tumor nodes <10 mm
CR	Not all evaluated	No	PR	
PR	Non-PD/	No	PR	

Table 10. Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
	not all evaluated			
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non-target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

12.2.6 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. The iRECIST time-point and best overall responses will be recorded separately.

Confirming progression: Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression) (Seymour et al, 2017). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as

evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
    - Continued unequivocal progression in non-target disease with an increase in tumor burden.
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD (Seymour et al, 2017, Table 2).

New lesions:

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 11. Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**, ***
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 decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD).
iUPD	Non-iCR/ Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD.
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD con-firmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD con-firmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and/or • previously identified NT lesion iUPD (need not be unequivocal) and/or • size or number of new lesions previously identified
Non-iUPD/ PD	Non-iUPD/ PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified.

* Using RECIST v1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same.
** in any lesion category.
*** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table 12. iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD,iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD,iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required.

- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

12.2.7 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

12.2.8 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.*, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion."

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (*e.g.*, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (Eisenhauer et al, 2009). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

13. STUDY APPROVAL, OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

13.2 Quality Assurance

The MCC places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translation research. The MCC Quality Assurance (QA) Office oversees the maintenance of quality standards in clinical cancer research through clinical data monitoring of Investigator-Initiated Trials (IITs) and routine audits.

13.2.1 Data Monitoring

The MCC QA Office will collaborate with the PI, Biostatisticians and Lead OnCore® Data Management Specialist in creating a Clinical Data Monitoring Plan (CDMP) using a risk based approach. The CDMP will describe the scope, communication plan, and frequency of monitoring visits as well as describe query submissions and resolutions, action items and monitoring reports. The QA monitor assigned to the trial will perform the monitoring tasks in accordance with the protocol specified CDMP. The monitoring process will provide research staff and PI with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of the case report forms, assure that all protocol requirements, including applicable regulations and investigator's obligations are being fulfilled, and prompt resolution of any inconsistencies in the study records.

13.2.2 Audit

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the

MCC Audit Committee will conduct a quality assurance audit. A minimum of 10% of patients enrolled in the study may be selected for review. The purpose of a MCC audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

13.3 Data and Safety Monitoring Committee

The MCC Data and Safety Monitoring Committee (DSMC) will oversee the conduct of this trial. The MCC DSMC performs routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs). The MCC DSMC will conduct review of the trial on a schedule determined the MCC Protocol Review & Monitoring Committee (PRMC). The MCC DSMC will monitor the following elements of the trial: adverse event analysis, serious adverse events, protocol deviations/violations, and accrual. In addition, when applicable will review QA audits and monitoring reports, previous reviews by the DSMC, suggested actions by other committees, such as the IRB, UK Risk Management Committee, and other parameters and outcomes as determined by the DSMC. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The MCC DSMC has the authority to amend, temporarily suspend, or terminate the trial based upon patient safety or compliance matters.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Sections 7, 8, 10 (& APPENDICES D AND E).

13.4 Data Reporting

13.4.1 Method

This study will require data submission and reporting via the OnCore Enterprise Research Clinical Trials Management System, which is the official database of the Markey Cancer Center. Instructions for submitting data is listed in study-specific guidance documents authored by a member of the MCC Data Management Team. These guidance documents may include any of the following, as appropriate for the scope of the study: eCRF Completion Guidelines, Data Management Specifications, Subject Console Guide, and Query Resolution Guide. These guidance documents will be approved and housed within OnCore to ensure access to approved versions to facilitate data submission.

13.4.2 Responsibility for Data Submission

This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. Study staff are responsible for submitting study data and/or data forms to OnCore as per the Markey Cancer Center SOPs. Study staff are responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

13.4.3 Publications of data and protection of trade secrets

The Principal Investigator holds the primary responsibility for publication of the study results; provided that the Principal Investigator will provide Exelixis with a copy of any proposed publication or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide

presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts and also comply with any provisions regarding publication that are agreed to between the Principal Investigator's institution (e.g., institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

13.5 Data Management

Data management will be performed by cross-team members at MCC. These team members will include representatives from the Data Management Team, Biostatistics and Bioinformatics SRF, and the Quality Assurance Office. They will work closely with study staff to ensure timely and accurate data submission. A protocol specific Data Management Plan (DMP) will be authored by a senior data manager in collaboration with the biostatistician and Principal Investigator with each expected to review and approve the finalization of the DMP. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol-specific DMP will additionally define the schedule at which data will be accessed by data management and study statistician to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, annual reports, interim analysis and final data analysis.

13.6 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRO. The PI is also responsible for notifying the Data and Safety Monitoring Committee of the MCCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities. DSMC will review all adverse events of this IIT as per its SOP.

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APPENDIX A. ECOG PERFORMANCE STATUS

Table 13. ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B. CABOZANTINIB MED LOG

PATIENT'S MEDICATION LOG – PAGE 1 OF 2

Today's Date _____ **Agent** ___Cabozantinib__ **Cycle #** _____

Patient Name _____ ***(initials acceptable).*** **Patient Study ID** _____

INSTRUCTIONS TO PATIENTS

1. Complete Medication Log. The med log form, also called a "pill diary", covers Day 1 thru Day 21.
2. You will take your prescribed dose of Cabozantinib ***once*** **daily** by mouth with water (at least 8 oz.), **approximately 2 hours after your evening meal (or** 1 hour *before* your evening meal**)**.
   You will take either ____ 40 mg tablet daily **OR** ____ 20 mg tablets daily.
3. Doses should be taken at approximately the same time each day.
4. Each dose **must be swallowed**. DO NOT chew or crush this medication.
   Do not eat grapefruit or Seville oranges when taking Cabozantinib.
5. *If you vomit your daily Cabozantinib dose*: Vomited doses **should not** be made up.
6. *If you forget to take your daily dose*: you should not make up any missed doses if more than 12 hours have passed after the time you would usually take Cabozantinib.
   If you miss a dose, **DO NOT TAKE** 2 doses at once to make up for the missed Cabozantinib dose.
7. On your medication log: Record the date, number of tablets you took, and what time you took them.
   If you have comments or notice any side effects, please record them in the Comments column.
8. Please return the forms to your physician when you attend your next appointment.

Day	Date	What time was Cabozantinib dose taken?	# of ___mg tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				

14				
15				
16				
17				
18				
19				
20				
21				

Your Physician's Office will complete this section below:

1. Date patient started protocol treatment:_____

2. Date patient was removed from study: _____

3. Patient's planned total daily dose: _____

4. Total number of pills taken this month: _____

Staff Signature: _____

APPENDIX C. LAB MANUAL: PDAC ORGANOID CULTURES

Protocol for Establishing Human PDAC Organoid Cultures from a Tumor Specimen

Notes:
This protocol describes methods to establish tumor organoid cultures from human pancreatic cancer specimens. These specimens are obtained from endoscopic biopsies and surgical resections of pancreatic neoplasms and are usually delivered in a 5 mL or 15 mL tube, respectively, containing Human Wash Medium supplemented with GlutaMAX, HEPES, and Primocin. The specimens should be processed as soon as possible to prevent autolysis or degradation. Except for digestions, all procedures should be performed on ice. The protocol is written for generating organoids from tumor specimens, but the same procedure can be followed to generate organoids from adjacent normal tissue as long as the Human Complete Feeding Medium is supplemented with 1 μM PGE2.
All human experiments are approved by the IRB of UKY, and written informed consent from the donors for research use of tissue is obtained prior to acquisition of the specimen. All the procedures should be performed on ice (unless otherwise specified) under sterile conditions by using sterile tools and by operating in a biological hood.

Reagents and Equipment: Human tumor (or adjacent normal) specimen
10.5 mM Rho Kinase Inhibitor (Y-27632) Stock
AdDF Wash Medium containing 2.5%FBS

Human Digestion Medium

Sterile scalpels
Sterile forceps
P2, P20, P200, P1000 pipettes and sterile tips
(For CAF isolation) 6 well culture dish
5 mL Protein LoBind Tubes
Sterile serological pipettes (5, 10, and 25 mL)
Timer
Mr. Frosty freezing container
37ºC water bath
Tissue culture hood with aspirator
Hot water flask pre-warmed to 37 ºC
37ºC tissue culture incubator
Recovery Cell Culture Freezing Medium

Human Complete PDO Medium

10 mg/mL DNAse I stock
Growth Factor Reduced Matrigel, Phenol Red Free on ice
ACK (Ammonium-Chloride-Potassium) Lysing Buffer

Ice bucket with ice
Sterile 10 cm tissue culture dish
Sterile aspirator pipettes
Cryovials
15 and 50 mL conical tubes
Pre-warmed 24 well culture plates

Small dewar with liquid nitrogen
Pipet-Aid/Pipette controller
-80ºC freezer
Refrigerated 15/50 mL tube centrifuge
Incubated rocker/rotator set to 37ºC
Liquid nitrogen cryofreezer

Procedure:

1. At least 6 hours before organoid isolation, place a 24-well plate in a 37 ºC tissue culture incubator.

2. Thaw an aliquot of the Human Digestion Medium in the 37 ºC water bath and bring temperature to 25-37 ºC.

3. Add 10 µL of 10 mg/mL DNAse and 10 µL 10.5 mM Y-27632 to the 10 mL aliquot of Human Digestion Medium (to final concentrations of 10 µg/mL and 10.5 µM, respectively).

4. Aliquot 3 mL of pre-warmed Human Digestion Medium supplemented with DNAse and Y-27632 to a 5 mL protein LoBind tube.

5. Record all the information available for the specimen, including: nosography, hospital, sample identifier, date, and the names of the people processing the sample.

6. Using sterile forceps, transfer the specimen to a sterile petri dish.

7. Examine the tissue macroscopically, and record the size, shape and gross morphological characteristics. *Since the handle of the scalpel contains centimeter markings, this can be used to measure the specimen.*

8. If adjacent normal tissue is visible on tumor specimen, carefully dissect this tissue away from the tumor tissue.

9. If the specimen is large enough, take a central piece of tumor tissue and put into a 15ml tube with 10% formalin for fixation and histological staining.

10. Mince the remaining specimen into small fragments (1 mm3 or less) using sterile scalpels.
    a. If there is fat present, try to dissect it away from the specimen.
    b. Note that pancreatic tumors are highly fibrotic, and therefore, the tissue is usually hard.

11. Take a few pieces and place into a cryovial, labelled with the organoid ID, “p0” (indicating that vial contains primary tissue), the date, and your initials. Snap freeze cryovial in liquid nitrogen.

12. Transfer remaining tissue to 5 mL protein LoBind tube containing the 3 mL Human Digestion Medium supplemented with DNAse and Y-27632.

13. Place the tube in rotating incubator set to 37 ºC with rapid rotation (35 rpm) for an initial digestion of 15 minutes.

14. Using a P1000 pipette set to 1000 uL, prewet the tip by pipetting Human Wash Medium a few times, and then triturate the digested tumor 10 times.

15. Allow the tube to sit for 1 minute so the larger tissue pieces can settle to the bottom.

16. Transfer the supernatant in a separate LoBind tube, labeled “Fraction 1.”

17. Add Human Wash Medium to Fraction 1 to fill tube to 5 mL total volume.

18. Centrifuge Fraction 1 at 200 RCF for 5 minutes at 4 ºC.

19. Carefully remove the supernatant from Fraction 1 without disturbing the cell pellet.

20. Resuspend the Fraction 1 pellet in 2 mL AdDF Wash Medium and store on ice.

21. Add 3 mL Human Digestion Medium supplemented with DNAse and Y-27632 to the remaining undigested tissue pieces leftover from the first digest.

22. Repeat steps 13-21 to acquire "Fraction 2," and (if there is sufficient undigested material to continue)

23. Combine all fractions together in one 5 mL protein LoBind tube, and fill tube to 5 mL with AdDF Wash Medium.

24. Add 5 mL AdDF Wash Medium to the remaining, undigested tissue fragments.

25. Centrifuge the tube of combined fractions and the tube of undigested tissue fragments at 200 RCF for 5 minutes at 4 ºC.

26. Place Human Complete Feeding Medium at 37 ºC to warm.

27. Carefully remove the supernatants from each tube without disturbing the pellets.

28. In very rare cases, large numbers of red blood cells might be seen in the pellet of combined fractions, coloring entire pellet red. If this is the case, perform ACK Lysis of red blood cells as follows. If no or minimal numbers of red blood cells are present, proceed with the next step.

a. Add 4 mL of room temperature ACK lysing buffer and let sit at room temperature for 1 to 2 minutes.

b. Invert and flick tube to resuspend the pellet and mix. Do not pipette up and down or cells will stick to the pipette.

c. Centrifuge the tube at 200 RCF for 5 min at 4oC.

d. Carefully aspirate the supernatant without disturbing the pellet.

e. Resuspend cells in 1 mL Human Wash Medium and then fill tube to 5 mL with additional 4 mL Human Wash Medium.

f. Centrifuge the tube at 200 RCF for 5 min at 4oC.

g. Carefully aspirate the supernatant without disturbing the pellet.

29. Resuspend the pellet of combined fractions in Matrigel. The volume of Matrigel to use will depend on the size of the pellet. It is best to err on the side of resuspending the pellet in less Matrigel to keep the cells concentrated, rather than diluting the material too much. As a ballpark estimate, a tumor pellet around 25 µL in volume would be resuspended in 800 µL Matrigel.

30. Plate 50 µL Matrigel domes into a pre-warmed 24 well plates. To aid in dome solidification, plates can be placed on top of a hot water flask, while you are pipetting the domes.

31. Place the plate into a 37 ºC tissue culture incubator until RGF BME solidifies (~10 minutes).

32. Resuspend the pelleted undigested tissue fragments in Recovery Cell Freezing Medium. (The volume to resuspend in depends on the volume of the pellet.)

33. Aliquot the tissue fragments to cryovials.

34. Place cryovials in a Mr. Frosty freezing container and freeze cells overnight at -80 ºC. *After 24 hours, frozen cells can be moved to a liquid nitrogen freezer for long-term storage.*

35. Add 10.5 mM Rho Kinase Inhibitor (Y-27632) Stock (to final concentrations of 10.5 µM) to the Human Complete Feeding Medium. You will need 500 µL of medium per well plated. If generating adjacent normal organoids, the Human Complete Feeding Medium should also be supplemented with PGE2 (to final concentration of 1 µM).

36. Add 500 µL of pre-warmed Human Complete Feeding Medium supplemented with Rho Kinase Inhibitor (Y-27632) to each well of organoids.

37. Return plates of organoids to tissue culture incubator.
Optional: To isolate cancer associated fibroblasts:
38. Separate a portion of digest to a new 15 mL conical tube.

39. Centrifuge at 200 RCF for 5 min at 4 ºC.

40. Carefully remove the supernatant.

41. Resuspend pellet in Human CAF Medium.

42. Transfer to 1 well of a 6 well culture plate.

43. Place in 37 ºC tissue culture incubator. *Note: At future passages, very short trypsin incubations will help dissociate fibroblasts while keeping cancer cells attached. This method may be used to enrich for fibroblasts.*

APPENDIX D. LAB MANUAL: EXOSOMAL LIPIDS

Lipid Exosomal Analysis for Plasma

*excerpts below from Fan et al, 2018 (PMID: 30292300)

Blood collection

Ten mL samples of blood will be drawn into a purple top vacutainer containing K_2-EDTA (Becton-Dickson), inverted twice to ensure dissolution of the EDTA, and kept on ice immediately after blood draw. The whole blood will be separated into packed red cells, buffy coat, and plasma within 30 min of collection by centrifuging at 3500g for 15 min at 4 degrees C in a swing out rotor. All blood processing procedures were performed in a class II biosafety cabinet housed in a BSL category 2 laboratory. Plasma (0.7 mL) was aliquotted into 1.5 mL screw cap vials, flash frozen in liq. N_2, and stored at -80 degrees C until exosomal isolation. These collection and processing procedures were designed to minimize variations in plasma and exosome quality.

Exosome preparation

Exosomes were isolated from plasma by differential ultracentrifugation adapted from Baranyai et al (2015) and Koga et al (2005). 0.7 mL cleared plasma were placed in 5 x 41mm polyallomer ultraclear ultracentrifuge tubes on ice, and centrifuged for 1 h at 70,000 g at 4 degrees C in a SWTi55 swing out rotor (Beckman). The supernatant was recentrifuged at 100,000 g for 1 h at 4 degrees C, and the pellet was drained and resuspended in 0.7 mL cold PBS, and recentrifuged at 100,000 g for 1 h at 4 degrees C. The washed exosomal pellets were resuspended in 100 μL nanopure water, vortexed for 30 s and transferred to a fresh microcentrifuge tube. The ultracentrifuge tube was washed with another 100 mL of nanopure water, vortexed for 30 s and the wash was transferred into same microcentrifuge tube, using the same pipet tip. The combined exosome suspensions were then lyophilized except for a small portion that was used for characterization by particle size distribution analysis (see below). These nanoparticles are operationally defined as exosomes.

Lipid extraction for exosomes

The lyophilized EXO preparations were extracted for lipidic metabolites using a solvent partitioning method with CH_3CN:H_2O:$CHCl_3$ (2:1.5:1, v/v) as described previously [Fan et al chapter, sample preparation for metabolomics investigation, 2012, *https://doi.org/10.1007/978-1-61779-618-0_11*.]. The resulting lipid extracts were vacuum-dried in a vacuum centrifuge (Eppendorf), redissolved in 200 μL $CHCl_3$:CH_3OH (2:1) with 1mM butylated hydroxytoluene, which was further diluted 1:20 in isopropanol/CH_3OH/$CHCl_3$ (4:2:1) with 20mM ammonium formate for UHR-FTMS analysis.

Microparticle characterization

A small fraction (<1%) of each exosome preparation was characterized by size distribution analysis using a Nanosight 300 (Malvern Instruments), which provided the distribution of the
Stokes' radius (mean 60-66 nm) and the number density of the particles. The method eliminates very small particles, and provides a strongly peaked, narrow distribution at the expected size for exosomes.

UHR-FTMS analysis of exosomal lipids

High sample throughput (≤ 16 min total cycle time per sample, <7 min for MS1 portion) was achieved using the nanoelectrospray TriVersa NanoMate (Advion Biosciences, Ithaca, NY, USA) with 1.5 kV electrospray voltage and 0.4 psi head pressure. UHR-FTMS data were acquired from an Orbitrap Fusion Tribrid (Thermo Scientific, San Jose, CA, USA) set at a resolving power of 450,000 (at 200m/z) for MS1 full scans using 10 microscans per scan in the *m/z* range of 150-1,600, achieving sub ppm mass accuracy through <1200m/z in positive mode. AGC (Automatic Gain Control) target was set to 1e5 and maximal injection time was set to 100 ms. During the MS1 run, the top 500 most intense monoisotopic precursor ions were isolated via quadrupole using 1m/z isolation window and HCD (Higher Energy Collisional Dissociation) set at 25% collision energy was performed in positive mode for data-dependent MS2 at a resolving power of 120,000 (at 200 *m/z*) to obtain fragments for acyl chain assignment and neutral loss of specific head groups. The AGC target was set to 5e4 with maximal injection time of 500 ms. MS2 does not distinguish the sn1 and sn2 acyl positions of glycerolipids, nor the position of unsaturations in acyl chains and acyl branching.

Lipid assignment

The UHR-FTMS raw data were assigned by our (CESB) in-house software PREMISE (PRecalculated Exact Mass Isotopologue Search Engine) that compares UHR-FTMS m/z data against our metabolite *m/z* library (calculated with mass accuracy to the 5th decimal point) to discern all known lipid MF and their 13C isotopologues, including hypothetical lipids, while simultaneously taking into account all of the major adducts (here H^+, Na^+, K^+, NH_4^+) (Lane et al, 2008, 2009). An in-house developed natural abundance (NA) correction algorithm (Carrerr et al, 2013; Moseley, 2010] was applied to simultaneously examine the distribution of naturally occurring ^{13}C isotopologues of the unlabeled lipids to help verify the assigned molecular formulae, and to eliminate nonmonoisotopic ^{13}C isotopologues from further analysis. For statistical classification, we used only high accuracy monoisotopic *m/z* values that mapped to lipid molecular formulae, and multiple adducts of each were tracked throughout to avoid redundancy. Below, such *m/z* values are referred to as "lipid features", and neither molecular formulae nor lipid names were directly used.

The number of assigned lipid features will be assessed for each sample. After combining all samples into a master file, the results of lipid features will be summarized and described. Prior to multivariate statistical analyses, MS1 peaks arising from solvent blanks and known contaminants will be assessed and potentially removed from the lipid feature lists. As absolute intensities vary from sample to sample, the lipid features must be normalized. This is equivalent to estimating the mole fraction of each lipid feature present, and therefore can be used for determining relative changes in composition.

APPENDIX E. MANAGEMENT OF CABOZANTINIB-RELATED ADVERSE EVENTS

Table 14. Management of Diarrhea Associated with Cabozantinib

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

Table 15. Management of Hypertension Associated with Cabozantinib

Event	Management
Subjects NOT receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic)[a] and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <140 mm Hg systolic or <90 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per Investigator discretion. • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 140 mm Hg systolic or < 90 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic. • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive emergency[c]	• Discontinue cabozantinib treatment.

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

Table 16. Management of Palmar-plantar Erythrodysesthesia (PPE) associated with Cabozantinib

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, Cabozantinib should be reduced to the next lower dose level[a]. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt Cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue subject from study treatment if PPE does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPE, palmar plantar erythrodysesthesia.
[a] Permitted dose levels are defined by individual protocols.

Table 17. Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
Non-UC: ≤ 1 mg/mg (≤ 113.1 mg/mmol) **For UC**: ≤ 2 mg/mg (≤ 226.2 mg/mmol)	• No change in Cabozantinib treatment or monitoring
Non-UC: > 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol) **For UC**: (> 2 and < 3.5 mg/mg (> 226.2 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 unless otherwise approved by sponsor. • If UPCR > 2 mg/mg, repeat UPCR monitoring within 7 days and once per week. If UPCR < 2 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and canbe done within 1 week of first reading.)
All Tumor Types: ≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt Cabozantinib treatment pending repeat UPCR monitoring within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR monitoring, 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 UPCR until it remains < 2 mg/mg on two consecutive measurements. If UPCR monitoring is determined to be stable (< 20% change) for 1 month then continue with UPCR monitoring per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue Cabozantinib treatment

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

Table 18. Management of Hepatotoxicity Associated with Cabozantinib

Severity of Transaminase (ALT or AST) and total bilirubin Elevations	Management
If ALT or AST is within normal limits at baseline and increases to > ULN - 3.0 x ULN OR Total bilirubin increases to > ULN - 1.5 x ULN	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and adding supportive care as indicated.
If elevation of ALT or AST to > 3.0 - 5.0 x ULN (total bilirubin ≤ 2.0 x ULN) OR Total bilirubin increases to > 1.5 - 3.0 x ULN (ALT or AST ≤ 3.0 x ULN)	• Interrupt Cabozantinib if lasting longer than 1 week. • Restart Cabozantinib after lab abnormalities have resolved to CTCAE Grade ≤ 1 or baseline grade at the same dose level prior to dose interruption or one dose level lower at the discretion of the Sponsor.
If ALT or AST increases to > 5.0 to ≤ 8.0 x ULN, (total bilirubin ≤ 2.0 x ULN) OR Total bilirubin increases to > 3.0 x ULN (ALT or AST ≤ 3.0 x ULN)	• Interrupt Cabozantinib and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart Cabozantinib at a reduced dose after lab abnormalities have resolved to CTCAE Grade ≤ 1 or baseline grade. • Discontinue if lab abnormalities cannot be reversed despite interruption of Cabozantinib.
ALT or AST > 8 × ULN OR ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with DILI	• Discontinue Cabozantinib unless these laboratory abnormalities have recovered to Grade 1 or baseline level after an interruption and the Sponsor has approved reinstitution of Cabozantinib.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DILI, drug-induced liver injury.
Note: The guidance for dose modifications for bilirubin abnormalities applies only to subjects without Gilbert's Disease. Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there is less than a doubling in the aminotransferases from baseline and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. The following condition requires discontinuation of cabozantinib: Drug-related ALT or AST >3 × ULN in combination with total bilirubin >2 x ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).

APPENDIX F. MANAGEMENT OF PEMBROLIZUMAB-RELATED ADVERSE EVENTS

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the table below.

Table 19. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO combinations.

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Grade 4 or recurrent Grade 3	Permanently discontinue		

				• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Nephritis and renal dysfunction: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3, or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e].		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

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 the table below.

Table 20. 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 intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

	Participant is permanently discontinued from further study drug intervention.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

APPENDIX G. POTENTIAL DRUG INTERACTIONS WITH CABOZANTINIB

The Investigator should evaluate concomitant medications prior to initiation for potential drug interactions with Cabozantinib through the CYP3A4 pathway.

The table below shows examples of potential strong inhibitors and inducers of CYP3A4; **this table below is not all-inclusive**.

Please refer to the FDA website for the most up-to-date lists of substrates, inducers and inhibitors of selected CYP450 isozyme pathways: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

Table 21. Drug interactions with cabozantinib

Strong Inhibitors of CYP3A4	Strong Inducers of CYP3A4
Conivaptan	Carbamazepine
Diltiazem	Efavirenz
Grapefruit Juice	Enzalutamide
Idelalisib	Erythromycin
Nefazodone	Mitotane
Anti-virals	Modafinil
Boceprevir	Nevirapine
Cobicistat	Oxcarbazepine
Conivaptan	Phenytoin
Danoprevir	Rifampin
Dasabuvir	St. John's wort
Elvitegravir	
Indinavir	
Lopinavir	
Nelfinavir	
Ombitasvir	
Paritaprevir	
Ritonavir	
Saquinavir	
Telaprevir	
Tipranavir	
Anti-Fungals	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Antibiotics	
Clarithromycin	
Telithromycin	
Troleandomycin	