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Study Title:

Phase II Trial Evaluating the Safety and Efficacy of Atezolizumab in Combination with Cabozantinib for the Treatment of Metastatic, Refractory Pancreatic Cancer

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Protocol Version(s) and Date(s)

Version 5– 10/15/2024

Investigator Agreement

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

Signature

Date (MM/DD/YY)

Name of Principal Investigator

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1. INTRODUCTION / SYNOPSIS

Pancreatic cancer is one of the leading causes of cancer deaths in the United States with limited treatment options, especially for those patients with metastatic disease. Combination treatment with cabozantinib and atezolizumab, has demonstrated safety for the treatment of other cancers and has shown promise in preclinical studies utilizing patient derived pancreas organoids. In this study, patients with refractory, metastatic pancreatic cancer will receive combination cabozantinib + atezolizumab and the efficacy of this treatment will be assessed through overall response rate (ORR), disease control rate (DCR), median overall survival (mOS), and median progression free survival (mPFS). Safety and tolerability of combination cabozantinib plus atezolizumab in metastatic pancreatic cancer patients will also be assessed and immune profiling pre- and post-treatment will be explored.

1.1 Phase

Phase II, single-center, single-arm study.

1.2 Indication

Refractory, metastatic pancreatic cancer.

1.3 Primary Endpoint

Overall response rate (ORR) or stable disease (SD) at 9 weeks in patients with refractory metastatic pancreatic cancer of cabozantinib plus atezolizumab.

1.4 Secondary Endpoints

Adverse Events and Toxicities according to CTCAE version 5.0 and summarized using descriptive statistics.

Disease control rate in patients with refractory, metastatic pancreatic cancer treated with combination cabozantinib plus atezolizumab

Median OS and mPFS in patients with refractory, metastatic pancreatic cancer treated with combination cabozantinib plus atezolizumab.

1.5 Exploratory Endpoints

Immune profiling of tissue and/or blood collected from patients with refractory, metastatic pancreatic cancer pre- and post-treatment with combination cabozantinib plus atezolizumab.

Quantified apparent diffusion coefficient (ADC) values of tumors pre- and post-treatment with combination cabozantinib plus atezolizumab.

T2 mapping of tumors pre- and post-treatment with combination cabozantinib plus atezolizumab.

1.6 Patient Population

Patients with refractory, metastatic pancreatic cancer who have received at least one line of prior systemic therapy for metastatic disease.

2. STUDY DESIGN

2.1 Phase

Phase II, single-center, single-arm study

2.2 Number of centers

Single Center: University of Arizona Cancer Center

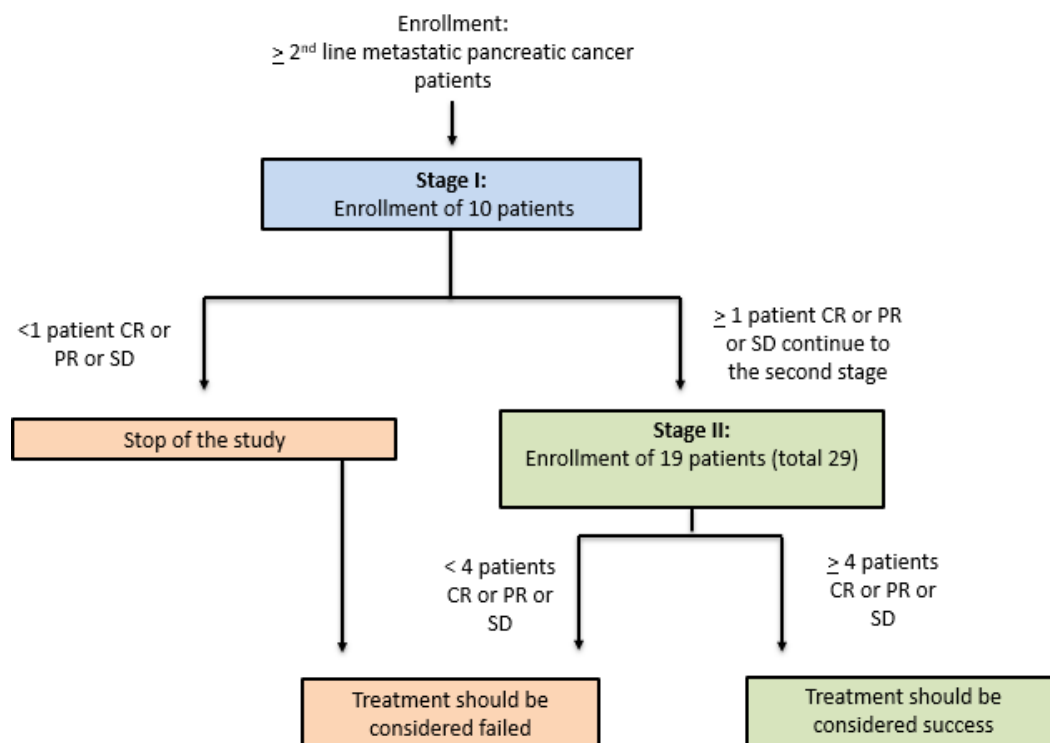
2.3 Number of subjects

Up to 29 subjects will be enrolled.

2.4 The subject participation time period

Subjects will be treated for 3 cycles (21 days/cycle), at which time they will be assessed for response. Treatment shall continue until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 15. Subjects will be followed long-term for survival outcomes.

Study Schema:



3. OBJECTIVES

3.1 Primary Objective

To evaluate the efficacy of cabozantinib plus atezolizumab in patients with refractory metastatic pancreatic cancer.

3.2 Secondary Objectives

To evaluate the safety of cabozantinib plus atezolizumab in patients with refractory metastatic pancreatic cancer

To assess the disease control rate (DCR) in patients with refractory metastatic pancreatic cancer treated with combination cabozantinib plus atezolizumab.

To further define survival outcomes of median overall survival (mOS) and median progression free survival (mPFS) in patients with refractory metastatic pancreatic cancer who receive combination therapy with cabozantinib plus atezolizumab.

3.3 Exploratory Objectives

To explore the immune effects of cabozantinib plus atezolizumab in patients with refractory metastatic pancreatic cancer.

To evaluate tumor response through comparison of baseline and post-treatment tumor quantified apparent diffusion coefficient (ADC) values.

To quantify T2 signal within the tumor using T2 mapping.

4. BACKGROUND AND RATIONALE

4.1 Disease/Condition

Pancreatic cancer is one of the leading causes of cancer deaths worldwide with a 5-year survival rate between 9 and 10%.^{1,2} Pancreatic cancer is often not diagnosed until advanced stages when patients are no longer candidates for curative resection. For patients with metastatic pancreatic cancer and good performance status, the current standard of care first-line treatments are FOLFIRINOX, gemcitabine with albumin-bound paclitaxel and gemcitabine with cisplatin for those with known *BRCA1/2* or *PALB2* mutations. For those patients with pancreatic cancer and a poor performance status, standard of care is limited to gemcitabine, capecitabine, or continuous 5-fluorouracil infusion.³ Second-line treatments are extremely limited with current recommendations to use treatments not selected in the first line.⁴⁻⁶ Recently, combination nanoliposomal irinotecan with fluorouracil and folinic acid was approved for use in patients who have progressive disease while on gemcitabine-based treatment.^{6,7} While there was a survival benefit with a median overall survival of 6.2 months for this combination, there is an associated increased risk of toxicity as well as increased cost.^{4,7} More therapeutic options are needed for this refractory population characterized by poor prognosis and limited treatment options. Future directions for treatment indicate that targeted molecular inhibitors of the tyrosine kinase pathway in conjunction with immune therapy may improve response rate.⁸

Numerous studies have explored the role of immunotherapy in advanced pancreatic ductal adenocarcinoma (PDAC) with dismal results.⁹ Pembrolizumab, a PD-1 checkpoint inhibitor, is approved for single-agent use in patients whose pancreatic cancer is microsatellite instability (MSI) high.¹⁰ In the phase II study of pembrolizumab for non-colorectal MSI high cancer, the objective response rate (ORR) for all patients was 34.3% (95% CI: 28.3% to 40.8%).¹¹ However, these genetic mutations are found in only approximately 1-3% of pancreatic cancer patients and the ORR for pancreatic cancer patients in the phase II trial was only 18.2% (95% CI: 5.2% to 40.3%).^{11,12} Further investigation of pembrolizumab in combination with gemcitabine and nab-paclitaxel for chemotherapy naïve patients demonstrated slightly improved efficacy over gemcitabine and nab-paclitaxel alone. However, the study only included chemotherapy-naïve patients rather than those who are refractory to treatment, and failed to meet its primary efficacy endpoint of >15% complete response.¹³ Another PD-1 checkpoint inhibitor, nivolumab has demonstrated safety in combination with gemcitabine and nab-paclitaxel for patients with advanced pancreatic cancer.^{14,15} The PD-L1 checkpoint inhibitor, durvalumab with or without the anti-CTLA-4 agent tremelimumab was found to be well-tolerated but lacked efficacy for patients with PDAC.¹⁶ Tremelimumab was investigated in combination with gemcitabine for the treatment of chemotherapy-naïve advanced pancreatic cancer and the combination was tolerable.¹⁷ Additionally, a phase 2 trial of single ipilimumab, an anti-CTLA-4 agent, for locally advanced or metastatic pancreatic adenocarcinoma had no responders.¹⁸ Another study investigating the combination of ipilimumab with gemcitabine found that while the combination is safe, adding ipilimumab

to gemcitabine does not appear to improve outcomes.¹⁹ While immune check-point inhibition alone or in combination with chemotherapy has yet to yield significant efficacy results, there remain future treatment directions including combination of immune checkpoint inhibitors with small molecule inhibitors such as our preclinical data suggesting promising efficacy with the combination of the PD-L1 checkpoint inhibitor atezolizumab with the multiple receptor tyrosine kinase inhibitor, cabozantinib.

4.2 Investigational Products

Cabozantinib

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs). It is provided as both capsules and tablets, but the two formulations are not interchangeable. Cabozantinib capsules (140 mg) are approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq® US PI and European Medicines Agency [EMA] SmPC). Cabozantinib tablets (60 mg) are approved in the United States, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx® US PI and EMA SmPC). Cabozantinib tablets (60 mg) have also been approved in the US, EU, and other regions for the treatment of hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib (Cabometyx US PI and EMA SmPC).

The targets of cabozantinib include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely hepatocyte growth factor (HGF) receptor (MET), vascular endothelial growth factor receptor 2 (VEGFR2, also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely-related RTKs KIT and FLT3. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis.

Refer to the Cabozantinib Investigator's Brochure for details on nonclinical and clinical studies.

Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity.^{20,21} Atezolizumab has minimal binding to Fc receptors,

thus eliminating detectable Fc–effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Atezolizumab is approved for the treatment of Alveolar Soft Part Sarcoma (ASPS), non-small cell lung cancer, small-cell lung cancer, hepatocellular carcinoma and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

4.3 Preclinical Experience

Preclinical data from the laboratory of Yana Zavros, PhD in pancreas organoid models suggests synergy when the tyrosine kinase inhibitor, cabozantinib is combined with the anti PD-L1, nivolumab (Unpublished Data, 2019). Our independently developed PDAC organoid protocol has been refined such that our cultures may be: 1) rapidly grown and tested to inform clinicians of patient treatment within 3 days of tissue procurement, 2) passaged indefinitely to enrich for the stem cells, and 3) co-cultured with the patient's own immune cells. The latter is advantageous because it allows us to study the interaction between the cancer cells and the immune cell compartment within the patient's own tumor microenvironment.

Figure 1A and B represents an example of one normal and one tumor organoid line clearly demonstrating morphological differences between these. While organoids derived from normal pancreatic tissue exhibit a spherical morphology lined with ductal epithelium (Figure 1A), PDAC organoids appeared lobular and irregular (Figure 1B). We established a PDAC patient-derived autologous organoid/immune cell co-culture (Figure 1C-E). Immunofluorescence showed the direct contact between CTLs and PDAC organoids (Figure 1E). In patients with an advanced stage tumor, there was a statistically significant increase in the infiltration of granulocyte-like myeloid-derived suppressor cells (G-MDSCs; CD45⁺HLA-DR⁻CD33⁺CD11b⁺CD14⁻, CD15⁺) within the tumor tissue compared to that of patients with a lower stage tumor (Figure 1F, G). Similarly, flow cytometric characterization of monocytes co-cultured with organoids derived from patients with a low stage tumor revealed a significantly higher monocytic myeloid-derived suppressor cell (M-MDSC) phenotype (Figure 1G). However, monocytes co-cultured with organoids derived from patients with an advanced stage tumor exhibited a significantly higher G-MDSC phenotype (Figure 1G).

In an autologous organoid/CTL co-culture derived from patients with a low stage tumor, organoids were sensitive to chemotherapy and nivolumab (PD-1Inh) treatment (condition 6, Figure 1I), whereby the addition of MDSCs did not affect PD-L1 expressing cell death (condition 8, Figure 1I). In these co-cultures, analysis of CD8⁺ T cell proliferation by a CFSE-based flow cytometric assay revealed increased CTL proliferation (Figure 1J). In contrast to organoids derived from patients with low stage

tumors, an organoid/immune cell co-culture derived from patients with an advanced stage tumor, exhibited insignificant organoid cell death when cultures were treated with nivolumab (PD-1Inh) in combination with chemotherapy (condition 6, Figure 1K). Importantly, the inclusion of MDSCs in these co-cultures hindered the efficacy of checkpoint inhibition by nivolumab resulting in increased PD-L1 expressing cell viability (condition 8, Figure 1K). Depleting the co-culture of MDSCs with the addition of cabozantinib (cabo) maximized the efficacy of checkpoint inhibition and significantly increased PD-L1 expressing cell death (condition 9, Figure 1K). Importantly, PD-L1 expressing cell death in response to combination treatment correlated with significantly increased CTL proliferation (Figure 1I). Figure 1H is a schematic diagram summarizing the composition and treatments of key co culture conditions 3, 6, 8 and 9. All experimental co-culture conditions are not shown (Zavros Lab, *Submitted for publication*).

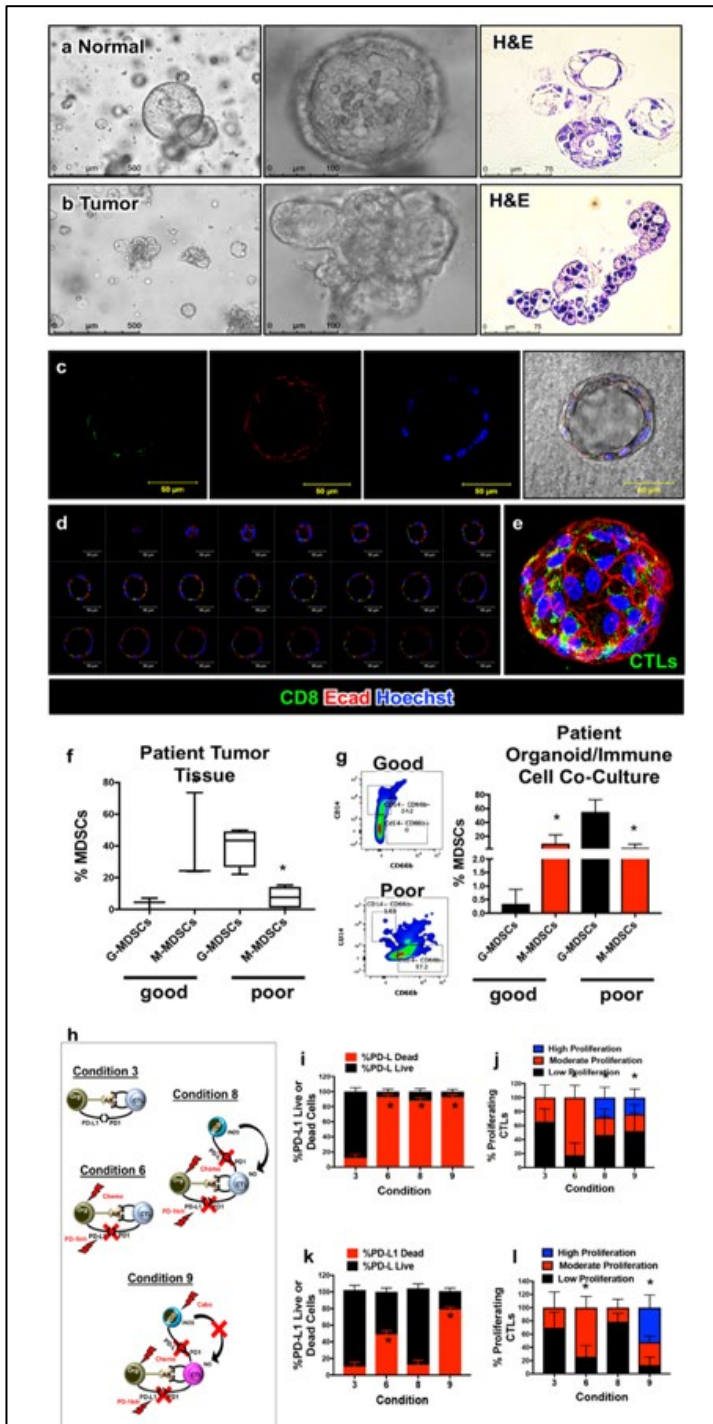


Figure 1: Generation and use of human-derived PDAC organoid/immune cell co-cultures. Light micrographs and H&E staining of (A) normal and (B) PDAC organoids. (C) Immunofluorescence stain of human-derived autologous pancreatic cancer organoid/immune cell co-cultures with antibodies specific for CD8 (green), E cadherin (Ecad, red) and Hoechst (blue). (D) Gallery of images from a Z stack acquisition, and (E) a 3D image of a PDAC organoid with autologous CTLs. (F) CyTOF analysis of M-MDSCs and G-MDSCs using cell isolated from patient tumor tissue. (G) Flow cytometric analysis of G-MDSCs and M-MDSCs in a co-culture of autologous PDAC organoids and immune cells derived from patients with good or poor prognosis. (H) Schematic representation of experimental conditions 3, 6, 12 and 9 used in organoid/immune cell co-cultures. Organoid/immune cell co-cultures derived from patients with a good prognosis were analyzed for (I) percent of live/dead PD-L1-expressing human-derived PDAC organoids in co-culture with autologous immune cells. (J) Percent of proliferating CTLs in co-culture with autologous MDSCs and human-derived PDAC organoids. Organoid/immune cell co-cultures derived from patients with a poor prognosis were analyzed for (K) percent of live/dead PD-L1-expressing human-derived PDAC organoids in co-culture with autologous immune cells. (L) Percent of proliferating CTLs in co-culture with autologous MDSCs and human-derived PDAC organoids. *P<0.05 compared to condition 3.

Laboratory of Yana Zavros, PhD,
Unpublished Data, 2019.

4.4 Clinical Experience with combination

A current multicenter phase Ib study, COSMIC-021, is being completed in multiple tumor cohorts and the combination of cabozantinib plus atezolizumab, has been safe and well tolerated (NCT03170960).^{8,22-24} The majority of adverse events were of grade 1 or 2 in the dose escalation stage (n=12) of the study through August 2018 and no grade 4 or 5 AEs were reported. Following the dose escalation stage, 141 expansion stage subjects were assessed through January 2019 and the most frequently reported adverse events of any grade, regardless of causality were fatigue (30%), diarrhea (28%), decreased appetite (24%), AST increased (22%), ALT increased (21%), and dysgeusia (21%). This resulted in the selection of a recommended dose of 40mg of cabozantinib once daily and 1200mg IV of atezolizumab every 21 days.⁸

In the non-small cell lung cancer expansion cohort of the COSMIC-021 study, the combination of cabozantinib was found to have an acceptable safety profile with Grade 3/4 treatment related AEs occurring in 14 (47%) patients, and 1 (3.3%) grade 5 treatment related AEs of myocarditis and pneumonitis. Additionally, there was a confirmed overall response rate of 23% in this cohort.²⁴ In patients with urothelial carcinoma, the combination of cabozantinib plus atezolizumab had promising clinical activity with a confirmed overall response rate of 27% and an acceptable safety profile with grade 3/4 treatment related AEs occurring in 57% of patients without any grade 5 events.²² In a cohort of men with metastatic castration-resistant prostate cancer, this combination again demonstrated promising clinical outcomes as well as a tolerable safety profile. Overall response rate in this cohort was 33% and only one Grade 5 adverse event of dehydration occurred in a 90 year old.²³ Overall, this data from the COSMIC-021 trial helps establish the safety of the proposed combination therapy regiment of 40mg of cabozantinib once daily and 1200mg IV of atezolizumab every 21 days that will be used in this study of patients with refractory, metastatic pancreatic cancer.

5. INVESTIGATIONAL PRODUCT, INTERVENTION, DEVICE

5.1 Investigational Products

Cabozantinib

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

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		

Refer to the Investigator's Brochure/Pharmacy Manual for details on storage and handling of cabozantinib.

Atezolizumab

The atezolizumab 1200 mg drug product will be supplied in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

5.2 Investigational products supply

Cabozantinib will be supplied by Exelixis, Inc. specifically for the purpose of this study in 20 mg tablets.

Atezolizumab will be supplied by Genentech, Inc. specifically for the purpose of this study in single-use, 20-mL USP/Ph. Eur. Type 1 glass vials.

5.3 Investigational product, Intervention or Device Accountability

Cabozantinib IP Accountability

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

Atezolizumab IP Accountability

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements. All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

5.4 Storage, Preparation and Handling

Cabozantinib

Subjects will receive cabozantinib orally at a dose of 2 tablets of 20 mg once daily.

Cabozantinib tablets should only be taken whole by mouth and should not be cut, chewed, or crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity. Cabozantinib should not be taken with food (subjects should not eat for at least 2 h before and at least 1 h after taking cabozantinib) and should be taken with a full glass (at least 8 ounces or 240 mL) of water. If a dose is missed, the missed dose should not be taken less than 12 h before the next dose. Cabozantinib tablets should be stored at controlled room temperature and inventoried according to applicable regulations.

Refer to the Investigator's Brochure/Pharmacy Manual for further details on storage and handling of cabozantinib.

Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200mg on day 1 on each 21-day cycle until unacceptable toxicity or disease progression.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix IV. Atezolizumab infusions will be administered per the instructions outlined in the table below.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
- No premedication is permitted prior to the atezolizumab infusion. - Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. - Atezolizumab should be infused over 60 ($\pm$ 15) minutes. - If clinically indicated, vital signs should be measured every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 10) minutes after the infusion. - Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	- If the patient 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 measured within 60 minutes prior to the infusion. - Atezolizumab should be infused over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

Refer to the Atezolizumab Investigator Brochure/Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix II.

No dose modification for atezolizumab is allowed.

6. SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log (in the UACC OnCore system) of all potential (i.e. consented) study subjects, which will include as applicable demographics, informed consent, eligibility, on treatment, off treatment, follow up and off study dates.

6.1 Inclusion Criteria

1. Stage IV pancreatic adenocarcinoma, confirmed by histology or cytology (Note: the primary pancreatic adenosarcoma must be confirmed by histology or cytology. The stage IV metastatic disease does not necessarily need to be confirmed by histology or cytology).
2. Clinical and/or radiographic progression on and/or intolerance to and/or ineligibility for treatment with at least one of the following: a fluoropyrimidine or gemcitabine based chemotherapy treatment regimens.
3. Radiographically measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Images (MRI or CT Scan) must be completed within 28 days prior to treatment start.
4. Age ≥ 18 years.
5. Patients who progress on adjuvant treatment and develop metastatic disease within < 6 months of adjuvant therapy will be considered as having one prior line of treatment and may be eligible pending subject meeting all other inclusion/exclusion criteria.
6. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
 - a) Absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$ without granulocyte colony-stimulating factor support within 2 weeks.
 - b) White blood cell count $\geq 2500/\mu\text{L}$
 - c) Platelets $\geq 100,000/\mu\text{L}$ without transfusion.
 - d) Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
 - e) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN) with the following exceptions:

Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.

Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN.
 - f) Total bilirubin $\leq 1.5 \times$ ULN (for subjects with Gilbert's disease $\leq 3 \times$ ULN).

- g) Serum albumin ≥ 2.8 g/dl.
 - h) (PT)/INR or partial thromboplastin time (PTT) test $< 1.3 \times$ the laboratory ULN.
 - i) Serum creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation:
Males: $(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)$
Females: $[(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)] \times 0.85$
 - j) Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h urine protein ≤ 1 g.
7. For patients receiving therapeutic anticoagulation, they must have a stable anticoagulant regimen.
 8. No clinically significant hypertension as per treating physician or if hypertension, adequate control with anti-hypertensives.
 9. Negative hepatitis B surface antigen (HBsAg) test at screening.
 10. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
 - The HCV RNA test must be performed for patients who have a positive HCV antibody test.
 11. ECOG performance status ≤ 1 .
 12. Recovered to baseline or to CTCAE v5.0 $\leq$ Grade 1 treatment-related toxicity from prior therapies.
 13. At least two weeks since last dose of prior treatment.
 14. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 6 months after the last dose of study treatment.
 15. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman > 45 years-of-age in the absence of other biological or physiological causes. In addition, females < 55 years-of-age must have a serum follicle stimulating (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examinations, or medical history interview by study site.
 16. Ability to understand and the willingness to sign a written informed consent.

6.2 Exclusion Criteria

1. Prior treatment with cabozantinib.
2. Prior treatment with atezolizumab and/or CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.
3. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 28 days before first dose of study treatment.
4. Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 2 weeks before first dose of study treatment.
5. Radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks prior to first dose of study treatment after radiotherapy or at least 4 weeks prior to first dose of study treatment after major surgery (e.g., removal or biopsy of brain metastasis). Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.
7. Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:
 - a) Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
 - b) Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
 - a) Cardiovascular disorders:
 - i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.

- ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
 - iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose of study treatment.
 - iv. Subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with a stable dose of permitted anticoagulation (see exclusion criterion #6) for at least 1 week before first dose of study treatment.
- b) Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
- i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), 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.
9. 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.
10. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
11. The subject has tumor invading a major blood vessel (encasement of local vascular structures is not exclusionary).
12. History of leptomeningeal disease.
13. Uncontrolled tumor-related pain:
- a) Patients requiring pain medication must be on a stable regimen at study entry.
 - b) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

- c) Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
14. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures.
- a) Patients with indwelling catheters are allowed.
15. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium >ULN).
16. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix III for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
- a) Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
 - b) Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
 - c) Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
 - i. Rash must cover < 10% of body surface area.
 - ii. Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
 - iii. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
17. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
- a) History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
18. Active infection requiring systemic treatment with the following exceptions:
- a) Urinary tract infections.

- b) HCV on active treatment.
19. Patients with SARS-COV-2 infections with the following exceptions:
- a) Recovery from active symptoms 30 days prior to treatment start.
20. Known history of infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or a known positive test for tuberculosis due to tuberculosis infection.
21. Other clinically significant disorders as deemed by the investigator, that would preclude safe study participation.
- a) Serious non-healing wound/ulcer/bone fracture.
 - b) Uncompensated/symptomatic hypothyroidism.
 - c) Moderate to severe hepatic impairment.
22. Major surgery (e.g., laparoscopic nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks 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.
23. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment [add reference for Fridericia formula].
- 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.*
24. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.
25. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF- α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
- a) Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Principal Investigator confirmation has been obtained.

- b) Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- 26. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.
- 27. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation.
- 28. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment of within 6 months after the final dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- 29. Inability to swallow tablets.
- 30. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
- 31. Any other active malignancy at time of first dose of study treatment or diagnosis of another malignancy within 3 years prior to first dose of study treatment that requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- 32. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.
- 33. Prior allogeneic stem cell or solid organ transplantation.

6.3 Enrollment

All subjects who complete the screening period of the study will be registered and assigned a unique sequential subject identification number (i.e., 001, 002, 003... etc.). This number will be used to identify the subject throughout the clinical study and will be used on all applicable study documentation related to that subject. The subject identification number will remain constant throughout the study.

The written informed consent document(s) must be signed and personally dated by the subject or by the subject's legally authorized representative and completed to a fully executed informed consent document and processed per the institution standard operating procedures.

Before subjects may be entered into the study, a copy of the written institutional review board (IRB) approval of the protocol, informed consent form (ICF), and all other

applicable subject information and/or recruitment material must be on file at the institution.

7 STUDY PLAN

7.1 IP regimen

Cabozantinib will be administered orally via tablets at 40 mg once daily for each day of the cycle.

Atezolizumab will be administered at 1200mg IV on Day 1 of each 3 week cycle (q3w).

7.2 Concomitant Medications

- Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the end of treatment visit. All such medications should be reported to the investigator and recorded in the patient's medical records.

7.3 Permitted Medications/Treatments

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 7.4 and Appendix I and II) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see Appendix II).

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

Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 6.3.1.3.8). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended. Withhold cabozantinib for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution.

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
 - At the time of first dose of study treatment:
 - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
 - Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 7.2 for prohibited anticoagulants.
 - After first dose of study treatment:

- Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
- Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. See Appendix I for management of thromboembolic complications while on study. See section 7.4 for prohibited anticoagulants.
- Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used concomitantly with heparin or factor Xa inhibitors due to the increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines.

7.4 Excluded medications/treatments

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

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

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five drug elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

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

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin.²⁵
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to <http://www.qtdrugs.org> for a list of drugs which have the potential to prolong the QTc interval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.
- Systemic corticosteroids and TNF- α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF- α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the

alternatives are not feasible, systemic corticosteroids and TNF- α inhibitors may be administered at the discretion of the investigator.

7.5 IP Potential Drug Interactions and Effects of Food

Cabozantinib : Potential Drug Interactions and Effects of Food

Currently available data suggest that cabozantinib: (1) is not anticipated to markedly induce or inhibit CYP enzymes at clinically-relevant plasma concentrations; (2) is a substrate for CYP3A4; (3) may have the potential to inhibit the P-gp transport activity but is not a substrate of P-gp; and (4) is a substrate of drug transporter MRP2.

Cytochrome P450: Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib plasma concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided.

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

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

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. A case of a drug-drug interaction between cabozantinib and warfarin that may involve displacement of plasma protein bound drug has been reported in the literature.²⁶ Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses is not

allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions: In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.s

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g., cyclosporine, delaviridine, efavirenz, emtricitabine) should be approached with caution, and subjects taking MRP2 inhibitors should be monitored for AEs.

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

Food Effects: As food increases exposure levels of cabozantinib, subjects should fast (with the exception of water) for at least 2 h before taking their dose of cabozantinib. After the 2-hour fast, 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.

8 REQUIREMENTS FOR TREATMENT

8.1 Standard dose/treatment/device use

Cabozantinib will be administered orally via two 20 mg tablets (40 mg once daily) for each day of the cycle.

Atezolizumab will be administered at 1200mg IV on Day 1 of each 3-week cycle (q3w).

8.2 IP Dose Modifications, Treatment Interruptions, Delays and Discontinuation

General

Dose modifications, treatment interruptions, delays, and discontinuations of cabozantinib or atezolizumab will be independent of each other. If cabozantinib is held, atezolizumab may continue. If atezolizumab is held, cabozantinib may continue.

Cabozantinib

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 40 mg/day. Two dose reduction levels of cabozantinib are permitted (see “Dose Reductions of Cabozantinib” table).
- Dose modification criteria for cabozantinib are shown in the “Dose Modifications of Cabozantinib” table. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in the “Dose Modifications of Cabozantinib for Treatment-Related AEs” table, if the Investigator feels it is in the interest of a subject’s safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per Investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity, with approval from the Principal Investigator. In case treatment with cabozantinib is discontinued due to AEs attributed to cabozantinib, treatment with atezolizumab should continue until disease progression or unacceptable toxicity.

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

Dose Reductions of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
40-mg cabozantinib oral daily	20-mg cabozantinib oral daily	20-mg cabozantinib oral every other day (QOD)
20-mg cabozantinib oral daily	No dose reduction permitted	—
Cabozantinib will be discontinued if a daily dose of 20-mg cabozantinib (minimum dose) is not tolerated		

Dose Modifications of Cabozantinib for Treatment-Related AEs

Event	Management
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are <u>intolerable and cannot be adequately managed</u>	At the discretion of the Investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator and approved by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care .

<u>Note:</u> The dose delay and modification criteria for specific medical conditions are provided in Section 6.3.1.3.

Dose Reinstitution and Reescalation of Cabozantinib

If the subject recovers from his or her toxicities to CTCAE v.5.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose.

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the Investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue cabozantinib.

Re-escalation to the previous dose, (but not higher than 40 mg/day) may be allowed at the discretion of the Investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, renal).

Further information on Guidelines for Management of Potential AEs related to Cabozantinib is provided in Appendix I.

Atezolizumab

Dose modifications for Atezolizumab are not permitted.

Further information on Guidelines for Management of Potential AEs related to Atezolizumab is provided in Appendix II.

9 STUDY PROCEDURES

9.1 Screening

Potential subjects will enter the screening period of the study after a completely executed informed consent has been obtained.

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies. Please refer to study schedule in section 26 of this protocol for screening procedures.

9.2 Registration

All regulatory requirements must be in place prior to subject registrations.

Single center study subject identification numbers will begin with XXX (i.e., 001, 002, 003... etc.) and continue to be assigned sequentially.

9.3 On IP treatment/Intervention/Device

During the Treatment Period subjects will receive treatment until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 15. Subjects should be instructed to immediately inform the Investigator of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant and should be documented. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

Regular tumor assessments should be performed to determine if PD is present.

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

9.4 End of IP treatment/Intervention/Device

Subjects will return to the study site approximately 30 days after their last dose of treatment to complete end of study assessments. If applicable, the end of treatment and 30 day follow up assessments can be collected on the same day.

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

Subjects that complete the planned treatment portion of the study will have an off treatment visit. Please see study schedule in section 26.

9.5 Follow up

Procedures for follow-up visits will be conducted per the study schedule in section 26 of this protocol.

9.6 Early Treatment Termination

Termination is defined as patient being taken off both Cabozantinib and Atezolizumab. Patients who are terminated early will have end of study evaluation procedures conducted per the study schedule in section 26 of this protocol.

9.7 Off Study

Subjects will be considered off study when all planned treatment, early termination, and follow-up visits have been completed, unless death or withdrawal of consent to continue participation occurs. This off study visit will be conducted as per the study schedule in section 26 of the protocol.

10 CORRELATIVE STUDIES

10.1 Organoid Development and Immune Profiling

In addition to studying response rate and stable disease in metastatic pancreatic cancer patients receiving cabozantinib plus atezolizumab, the effects of cabozantinib plus atezolizumab on patient derived organoids will be evaluated. Pancreatic organoids retain much of the tissue architecture and physiological function of the pancreas with the additional benefit of an experimentally tractable system that allows for cell and genetic manipulation *in vitro*. Our unique co-culture model enables replication of the human tumor and microenvironment interaction, thus enabling investigation of the effects of cabozantinib and atezolizumab on both the tumor and immune compartments of patients enrolled on this study.

Each patient's PDAC organoid line is unique with regard to responsiveness to treatment, and the organoid response may reflect the patient outcome. Organoids will be derived from subjects using either resected tumor, endoscopic ultrasound-guided or interventional radiology guided core needle biopsies (Figure 2A). Autologous blood will also be collected and organoids co-cultured with isolated subject immune cells (Figure 2B, C) to establish tumor organoid/immune cell co-cultures. Data will be correlated with the patient's response to treatment *in vivo* (Figure 2F).

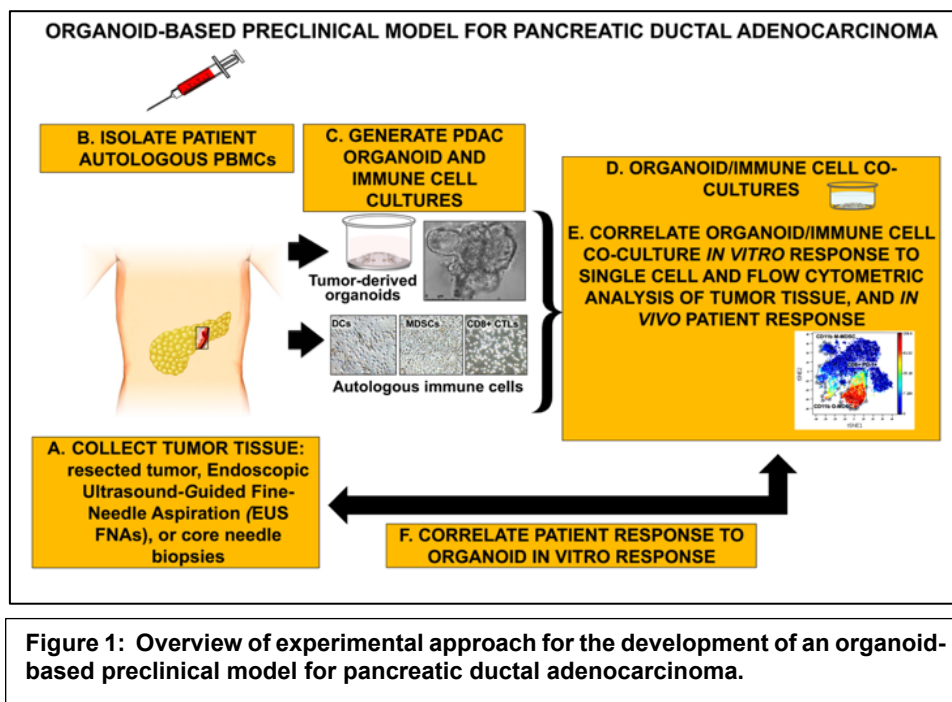


Figure 1: Overview of experimental approach for the development of an organoid-based preclinical model for pancreatic ductal adenocarcinoma.

Biopsies will be used for the generation of patient derived organoids (PDOs) and for target modulation. Autologous blood will also be collected and organoids co-cultured with isolated patient immune cells. PDO/immune cell co-cultures generated will be treated with cabozantinib and atezolizumab to assess correlation with clinical response. Baseline and on treatment biomarker analysis will be done using Aurora Cytex and NanoString DSP technologies. Multiparametric immune profiling by flow cytometry will be performed using the Aurora Cytex 5-laser system and validated immunophenotyping staining panels to perform high complexity deep immune cell profiling of peripheral blood mononuclear cells (PBMCs). This approach will enable comprehensive assessment of the immune response including detection of rare and dim populations not easily detected using other complex approaches. Similarly, single cell suspensions liberated from fresh tumor samples will be utilized to assess T-cell proliferation and infiltration and comprehensively profile the immune microenvironment changes after cabozantinib and atezolizumab treatment. We will also use the NanoString DSP on FFPE samples from these biopsies to demonstrate T-cell infiltration and localization and to better characterize the spatial interactions of the activated TME after cabozantinib and atezolizumab treatment. The majority of specimens will be from metastatic lesions. The analysis will focus on understanding the immune milieu and correlating it with our pre-clinical data. Importantly, the ability to rapidly grow PDOs, in the context of the patient's immunosuppressive cells and cytotoxic T lymphocytes, should allow us to predict each patient's response to cabozantinib and atezolizumab in the lab and correlate with patient outcomes as proof of principle.

The proposed use of the patient-derived organoid/immune cell co-culture is to screen for the sensitivity and efficacy of response to therapies. The proposed study is significant because patient-derived PDAC organoid/immune cell co-cultures may be used to screen for the sensitivity and efficacy of response to therapies. It is predicted that each patient's tumor organoids will be unique with regard to responsiveness to drug targets. Thus, increasing the efficacy of treatment for each individual patient will subsequently increase the survival and improve patient outcome.

10.1.1 Collection

Organoids will be derived from subjects using either resected tumor, endoscopic ultrasound-guided fine-needle aspiration biopsies, and/or core needle biopsies. Resected tumor and biopsies samples will be collected prior to treatment initiation and after the first 9 weeks (W10D1). An additional, optional biopsy can be performed after the end-of-treatment visit, after disease-progression.

Blood will be collected from the patient prior to treatment initiation (baseline), Week 10 Day 1, Week 13 Day 1 and every 3 cycles (9 weeks) thereafter, and at the end-of-treatment visit (after disease-progression).

10.1.2 Processing

Samples will be sent to the Zavros for processing after collection.

10.1.3 Storage

Processed samples will be stored by the Zavros lab.

10.1.4 Analysis

Immunofluorescence:

Organoids will be analyzed by whole mount immunofluorescence staining according to our previously published protocols 49, 50. Human-derived cultures will be immunostained using antibodies specific for HNF-1b, Sox 9 and CK19, PD-L1, CD11b, CD8 and/or EpCAM.

Flow Cytometry:

Organoids and immune cells will be dissociated from co-cultures using Accutase and cell viability analyzed using the LIVE/DEAD Viability/Cytotoxicity Kit. Organoid and immune cell co-cultures will be analyzed for CXCR3, CXCL9, CXCL10, EpCAM/PD-L1, CD8, CD11b, CD33, HLA-DR, Lin, CD15, CD14, CD66b and IL-4Ra. CD8+ T cell proliferation will be measured using a CFSE-based flow cytometric assay.

NanoString Digital Spatial Analysis (DSP):

Tumors will also be analyzed by DSP using the newly purchased instrument at the University of Arizona to identify changes in the immune cell population in response to the experimental treatments. An automated setup capable of imaging and sample collection was developed by modifying a standard microscope. For protein detection, a multiplexed cocktail of primary antibodies, each with a unique, UV photocleavable indexing oligo, and/or 1-3 fluorescent markers (antibodies and/or DNA dyes) can be applied to a slide-mounted FFPE tissue section.

10.1.5 Destruction

Samples will be stored for up to two years following completion of the study. If a subject withdraws consent from the study, their samples will be destroyed

10.2 Imaging Studies: T2 Analysis

This project may use non-FDA devices that are approved for use on the Banner Clinical scanner. Specifically, this project may use one or more of the following devices: Radial TSE.

10.2.1 Imaging Data Collection

The consented subject will be screened for any contraindications to MRI and magnetic materials. The investigator or MRI Technologist will explain the MRI system and the scan that the subject will take part in. The subject will be asked to lie down on the scanner bed. Some part of the subjects' body may be covered or enclosed within an FDA or UA HSPP approved MRI coil.

10.2.2 Processing and Analysis of Imaging Data

Processing and analysis software will be used to analyze the image data collected within this project. This software will not be used for any of the medical purposes listed in the International Medical Device Regulators Forum, *Software as a Medical Device*

(SaMD): *Key Definitions* document. In other words, the software will not be used for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- provide information by means of in vitro examination of specimens derived from the human body.
- provide means and suggestions for mitigation of a disease,
- provide information for determining compatibility, detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities,
- be an aid to diagnosis, screening, monitoring, determination of predisposition; prognosis, prediction, determination of physiological status.

Additionally, all software used to process and analyze image data collected during this project is used in “Exempted investigations” based on the Code of Federal Regulations Title 21 Section 812.2 (c)(3)(iv). In other words, the software

- is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

A Medical Device appendix will be submitted for any software used in this project that does not satisfy the above requirements.

11 DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan High Risk

11.1 Identification of the DSMB obligated for oversight responsibilities

The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a High Risk level by the DSMB.

11.2 Identification of the entity obligated for routine monitoring duties

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues. Real-time monitoring will be documented in a log that will be updated when a new or ongoing safety issue occurs. Updates will be reviewed with the PI weekly for review and signature.

11.3 Monitoring progress and data review process

Routine monitoring of subject data will be conducted at least every month.

The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility – 100% of cases, up to three subjects;
- Data review – 100% of cases, up to three subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable

data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms will be created to include study data points and the adverse event forms and be completed using the institution database or other acceptable data formats. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents will be conducted at least every six months, and routine monitoring of test article will be conducted at least every three months.

11.4 Process to implement study closure when significant risks or benefits are identified

In the first stage of the study, 10 subjects will be recruited. If no responses occur, the study will be stopped. The study may be stopped at any time at the discretion of the principal investigator if The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.

11.5 Description of adverse events and reporting procedures

11.5.1 Adverse Events

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pancreatic cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Any and all adverse events will be recorded on the UACC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

11.5.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- 1) Results in death;
- 2) Is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).;
- 3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
- 4) Results in disability persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions), or;
- 5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator may jeopardize the subject or that may require medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

11.6 Safety Plan

The safety plan for patients in this study is based on clinical experience with atezolizumab and cabozantinib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 11.6.1 and Section 11.6.2). Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study as indicated below. Administration of atezolizumab and the

first dose of cabozantinib will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Subsequent doses of cabozantinib will be self-administered at home. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix I for cabozantinib and Appendix II for atezolizumab. Refer to Section 12 for additional details on safety reporting (e.g., adverse events, pregnancies) for this study.

11.6.1 Risks Associated with Cabozantinib

Cabozantinib has been associated with risks such as the following: GI disorders, non-GI fistula formation, hemorrhage, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, hepatocellular toxicity, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders. Refer to [Appendix I](#) of the protocol and the Cabozantinib Investigator's Brochure for a detailed description of anticipated safety risks for cabozantinib.

11.6.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: Immune Related Reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial palsy, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to [Appendix II](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

11.6.3 Management of Patients Who Experience Adverse Events and Potential Overlapping Toxicities

Atezolizumab and cabozantinib have molecule specific safety profiles based on their mechanism of action and adverse events that may also overlap. These include but are not limited to, hepatotoxic, endocrine, gastrointestinal, dermatologic, neurologic, renal, and pulmonary events, as well as signs and symptoms such as fatigue and, decreased appetite that may be related to multiple system organ class events. The attribution of each drug in certain adverse events may be uncertain when the products are administered as combination treatment and warrant diagnostic work up. For the management of such potentially overlapping adverse events in patients treated with atezolizumab in combination with cabozantinib, adverse events should be managed according to the recommendations in [Appendix 1](#) (cabozantinib) and [Appendix 2](#) (atezolizumab) and applied to the component of the study treatment judged to be the primary cause. If individual component causality for adverse events cannot be determined, conservative management should be followed to include dose modification/interruption of both agents.

11.6.4 Methods and timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events are recorded on the Adverse Event CRF and reported in accordance with instructions provided in this section and in Section 12. For each adverse event recorded on the Adverse Event CRF, the investigator will assess seriousness, severity, and causality.

11.6.4.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event CRF. After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 11.5.2 for instructions for reporting serious adverse events). After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 11.7.

11.6.4.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

11.6.4.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living ^{b,c}
4	Life-threatening consequences or urgent intervention indicated ^d
5	Death related to adverse event ^d

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v{5}.0), which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
- Grade 4 and 5 events must be reported as serious adverse events

11.6.4.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Causality will be assessed individually for each protocol-mandated therapy.

Expected and Unexpected Events:

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

11.6.4.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event CRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the Adverse Event CRF.

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion related reaction") on the Adverse Event CRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction CRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event CRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction CRF.

Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF.
- If vomiting results in severe dehydration, both events should be reported separately on the CRF.

- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the CRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the CRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF.

All adverse events should be recorded separately on the Adverse Event CRF if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event CRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 12 for reporting instructions). The Adverse Event CRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events. A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event CRF.

Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 X ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event CRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event CRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g.,

"elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event CRF.

Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event CRF.

Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $> 3 \times \text{ULN}$ in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event CRF and reported immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest.

Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression pancreatic cancer should be recorded on the Death Attributed to Progressive

Disease CRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event CRF and immediately reported.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event CRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death"). Deaths that occur after the adverse event reporting period should be reported as described in Section 11.7.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions CRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Lack of Efficacy or Worsening of Pancreatic Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 11.5.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
 - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
 - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event CRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 11.5.2). In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population. For atezolizumab or cabozantinib, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab or cabozantinib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event CRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event CRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

Pregnancy

If a female subject or a female partner of male subject becomes pregnant while receiving the study drug or within 6 months after the last dose of study drug(s), a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
 - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
 - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

AESI specific to atezolizumab are:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis.
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

11.7 Adverse Events that Occur After the Reporting Period

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up CRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event CRF. However, if the EDC system is not available, the investigator should report these events directly to the DSMB.

11.9 Plan for assuring data accuracy and protocol compliance

Routine study activity and safety information will be reported to the DSMB on a monthly basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least quarterly.

11.6 Notification of the funding agency, as applicable

The PI will immediately notify, in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the SRC.

12 ADDITIONAL SAFETY REPORTING REQUIREMENTS

Exelixis Reporting Requirements

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 (Section 8.1)
 - The reason why the event is considered to be serious (i.e., the seriousness criteria) (Section 11.6.4.3)
- 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 the first dose of study treatment 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 or if the SAE occurs in screening.

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.

Pregnancy/Lactation Exposure

Use of highly effective methods of contraception is very important during the study and must continue for 4 months after the last dose of cabozantinib and 6 months after the last dose of atezolizumab. If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy and the infant should have follow up for at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, the Investigator will ask the pregnant female to consent to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth. Furthermore, male subjects must refrain from donating sperm in order to avoid transmission of study treatment in semen for the duration of study treatment and through 6 months after their last dose of study treatment. Both male and female subjects should seek advice and consider fertility preservation before receiving study treatment.

The Investigator must inform Exelixis of the pregnancy. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Females should not breastfeed while receiving study treatment and for up to 4 months from the last dose of cabozantinib and up to 6 months from the last dose of atezolizumab.

Genentech Reporting Requirements

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed Genentech approved reporting forms should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax : 650-238-6067

Email : usds_aereporting-d@gene.com

All Product Complaints without an AE should be called into the phone number below :

[Phone: 800-334-0290 \(M-F: 5 am to 5 pm PST\)](tel:800-334-0290)

[These single case reports \(initial and follow-up\) will be exchanged between the parties as outlined below so that regulatory obligation are met.](#)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

• **Other Special Situation Reports**

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

- **Product Complaints**

A product complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

- **Pregnancy reports**

If a female subject becomes pregnant while receiving atezolizumab or within 6 months after the last dose of atezolizumab, a report should be completed and expeditiously submitted to Genentech, Inc. While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via sponsor-investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by sponsor-investigator to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by sponsor-investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MedWatch 3500A Reporting Guidelines

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

- Protocol number and title description

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at <https://www.fda.gov/media/69876/download>

Post-Study Adverse Events

For studies involving collection of survival data the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

The principal investigator, will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The study PI/study sponsor will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review

Boards (IRB), where applicable. The site's local IRB can be contacted at: VPR-IRB@arizona.edu.

The study PI will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

Aggregate Reports

Development Safety Update Report

The University of Arizona Cancer Center and the Principal Investigator will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The sponsor-investigator, agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to The University of Arizona Cancer Center and the Principal Investigator an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees the sponsor-investigator may cross-reference the executive summary of the Genentech DSUR, as applicable.

Other Reports

The University of Arizona Cancer Center and the Principal Investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

anti-pdl-1-mpd3280a-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvistsa@gene.com

QUERIES

Queries related to the Study will be answered by sponsor-investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Genentech Product. Sponsor-investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Genentech Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that **the sponsor-investigator**, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If **sponsor-investigator** issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist **sponsor-investigator** with signal and risk management activities related to the Product within the Study.

Genentech will also provide **sponsor-investigator** with any new relevant information that may modify, or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

13. QUALITY ASSURANCE MEASURES

Per the UACC DSMB Charter, Internal *Ad Hoc* audits may be performed on any UACC clinical trial if identified for audit, the audit will be conducted by an identified audit team per the UACC DSMB Charter. A QA/QC representative will coordinate the audit team functions and a written audit report will be provided to the principal investigator and the DSMB.

14. RECIST CRITERIA

Clinical response, as reflected by response rate by RECIST 1.1 criteria, is the primary endpoints of this study. RECIST 1.1 criteria are described in detail at <http://www.recist.com>.

15. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational products.

Subjects that wish to discontinue active IP treatment may elect to continue with the other protocol required assessments. The investigator should discuss with the subject the options for continuation of the study schedule of assessments (i.e. blood work, scans, physical exams, diaries) and collection of data, including endpoints and adverse events.

Specific conditions necessitating removal of subjects include the following:

- An AE or intercurrent illness that in the opinion of the Investigator warrants the subject's withdrawal from study treatment.
- The Investigator believes it is not in the best interest of the subject to continue on study.
- Specific conditions described in Dose Modifications Section 8.2
- Necessity for treatment with other anticancer treatment prohibited by protocol.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the study and for 4 months after discontinuation of study treatment.
- Women who become pregnant or are breastfeeding.
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the Principal Investigator.
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment related AEs unless approved by the Principal Investigator.
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;

- Significant noncompliance with the protocol schedule in the opinion of the Investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the Investigator. Patients who continue study treatment beyond progression must be reconsented into the study.
- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, phone contact, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

16. STATISTICAL CONSIDERATIONS

In this Phase 2 single arm study, up to 29 metastatic pancreatic cancer patients who have received at least one line of prior systemic therapy will be enrolled. All patients will receive cabozantinib plus atezolizumab, with a hypothesis that the combination of cabozantinib and atezolizumab in patients with metastatic, refractory pancreatic cancer will improve response rate or stable disease at 9 weeks compared to historical controls.

For this study, An H_0 of 0.05 vs H_1 of 0.20 was assumed. The Simon optimum design recruits 10 subjects into the first stage; if ≥ 1 subject has a CR or PR or SD at 9 weeks, the study will then continue to the second stage. If there is no CR PR or SD, the trial will be stopped. The second stage will recruit an additional 19 subjects (total of 29). If ≥ 4 subjects have a CR or PR or SD, then treatment will be considered a success. This design has an alpha level of 0.05 and power of 0.80.

The proportion of patients with CR or PR or SD at 9 weeks will be estimated using 95% exact binomial confidence intervals. Overall survival and progression free survival will be estimated using Kaplan-Meier curves; median values will be reported with 95% confidence intervals. Safety will be assessed descriptively with tabulations of adverse events. Any serious adverse events will be reported in detail.

Statistical analysis of the immune data generated in the patient organoids will be primarily descriptive in nature. Comparison of the in vitro responses to treatment with the immune parameters will be performed using two sample t-tests (if normality is appropriate) or Wilcoxon Rank Sum Tests (in the absence of normality). Immune effects in the patients with CR or PR or SD versus those without will be estimated. Although the hypothesis is that we will observe > 4 patients with CR or PR or SD, we acknowledge that the sample size for the responders may be small. In those patients with optional post-treatment biopsies, the immune parameters will be compared using paired t-tests (assuming normality) or Wilcoxon Signed Rank Tests (in the absence of normality). Comparisons of baseline and post-treatment tumor quantified apparent diffusion coefficient (ADC) values will be performed using a similar approach. Estimation of the T2 signal parameters will be performed using 95% confidence intervals. A p-value < 0.05 will be considered statistically significant. There will be no adjustment for multiple comparisons, but borderline p-values will be cautiously interpreted.

17. ANALYSIS

17.1 Safety Analysis

For the safety analysis, all enrolled patients who receive at least one dose of cabozantinib and atezolizumab will have information collected on adverse events, which will be summarized by dose, severity as assessed by the Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0 and relationship to study drug.

The first safety analysis will be conducted when a subject completes the first treatment cycle of combination cabozantinib plus atezolizumab. Further analysis will be conducted at the completion of each subsequent cycle.

17.2 Efficacy Analysis

Participants will be evaluated for response after 9 weeks (End of Cycle 3) and every 9 weeks thereafter until disease progression or death from any cause, whichever occurs first. Response and progression will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

Efficacy will be assessed via ORR, SD, DCR, PFS, and OS as follows:

Overall Response Rate (ORR):

Overall response rate is defined using the RECIST 1.1 criteria as the proportion of subjects with an investigator-assessed partial or complete response (PR or CR).

Stable Disease (SD):

As defined using the RECIST 1.1 criteria, neither sufficient shrinkage (compared to baseline) to qualify PR or CR nor sufficient increase (taking as reference the smallest sum of diameters at baseline or while on study, whichever is smallest) to qualify for progressive disease (PD).

Disease Control Rate (DCR):

Disease control rate is defined as the percentage of patients who achieve complete response, partial response, or stable disease. DCR is the sum of the complete, partial and stable disease rates.

Progression-free survival (PFS):

Progression-free survival will be defined as the time from administration of the initial dose of cabozantinib and atezolizumab to evidence of radiographic progression as defined by RECIST criteria or death from any cause without evidence of disease progression, whichever occurs first.

Overall Survival (OS):

Overall survival will be defined as the time from administration of the initial dose of cabozantinib and atezolizumab until death from any cause.

18. REGULATORY OBLIGATIONS

18.1 Informed Consent

Before a subject's participation in the clinical study, the investigator or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures or investigational products are administered or initiated.

18.2 Institutional Review Board

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

19. ADMINISTRATIVE PROCEDURES

19.1 Investigator Responsibilities

The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

19.2 Data and Safety Monitoring Board Protocol Review

Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

Any protocol revision or amendment that includes a potential change to any section of data and safety monitoring plan must be reviewed and approved by the DSMB **prior to the protocol amendment submission to the IRB.**

19.3 Conditions for Modifying the Protocol

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the Principal Investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

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

19.4 Conditions for Terminating the Study

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

19.5 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..

20. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining,

analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

21. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

22. DATA

Applicable data as specified as required in the protocol will be reported/submitted in the case report form (CRF). Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. **CRFs will be completed via the UACC OnCore.**

Additional procedures and assessments may be performed as the institution's standard of care; however, these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product/intervention/device or employed as a control in the investigation.

23. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

The investigator should not implement any deviation from, or changes of, the protocol without prior review and documented IRB approval of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), change of telephone number(s)). A waiver of inclusion/exclusion criteria granted by the sponsor-investigator must be documented and IRB approved prior to implementation.

24. ECOG

The Eastern Cooperative Oncology Group performance score is determined based on the following scale:

Grade	ECOG Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	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	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

OR

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

OR

Karnofsky Description (age ≥ 16 years)		Lansky Scale (age < 16 years)	
100	Normal, no complaints, no evidence of disease.	100	Fully active.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restriction in physically strenuous play.
80	Normal activity with effort; some signs or symptoms of disease.	80	Restricted in strenuous play, tires more easily, otherwise active.
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restrictions of, and less time spent in active play.
60	Requires occasional assistance but is able to care for most of his/her needs.	60	Ambulatory up to 50% of time, limited active play with assistance/supervision.
50	Requires considerable assistance and frequent medical care.	50	Considerable assistance required for any active play, fully able to engage in quiet play.
40	Disabled, requires special care and assistance.	40	Able to initiate quite activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	Needs considerable assistance for quiet activity.
20	Very sick, hospitalization necessary.	20	Limited to very passive activity initiated by others (e.g., TV).
10	Moribund, fatal processes progressing rapidly.	10	Completely disabled, not even passive play.

25. COMMON TOXICITY CRITERIA (CTCAE)

CTCAE Version: 5.0

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

26. STUDY SCHEDULE

	Pre-treatment	Treatment					Post-treatment		
	Screening/ Baseline	W1 D1	W4 D1 ⁿ	W7 D1 ⁿ	W10 D1 ⁿ	W13 D1 and beyond ⁿ	Decision to end Treatment ^o	30-days Post- treatment ^{op}	Long-term Follow-up ^q
Informed Consent ^l	X								
Demographics ^l	X								
Height ^l	X								
Physical Examination ^m	X	X	X	X	X	Every 3 Weeks	X	X ^w	
Weight ^l	X	X	X	X	X	Every 3 Weeks	X	X ^w	
Vital Signs ^{mt}	X	X	X	X	X	Every 3 Weeks	X	X ^w	
ECOG PS ^m	X	X	X	X	X	Every 3 Weeks	X	X ^w	
Chemistry Panel ^{lam}	X	X	X	X	X	Every 3 Weeks	X	X ^w	
CBC with Differential ^m	X	X	X	X	X	Every 3 Weeks	X	X ^w	
Urinalysis/UPCR ^m	X	X	X	X	X	Every 3 Weeks	X	X ^w	
PT/INR/PTT ^m	X	X	X	X	X	Every 3 Weeks	X	X ^w	
TFTs ^{bl}	X	X	X	X	X	Every 9 Weeks	X	X ^w	
12-lead ECG ^{ms}	X	X	X	X	X	Every 9 Weeks	X	X ^w	
Pregnancy Test ^{cm}	X								
FSH ^{lr}	X								
HBsAg ^l	X								

	Pre-treatment	Treatment					Post-treatment		
	Screening/ Baseline	W1 D1	W4 D1 ⁿ	W7 D1 ⁿ	W10 D1 ⁿ	W13 D1 and beyond ⁿ	Decision to end Treatment ^o	30-days Post- treatment ^{op}	Long-term Follow-up ^q
HCV ^l	X								
Tumor Assessment ^{del}	X				X ^f	Every 9 Weeks ^p			
Cabozantinib Treatment ^g		Continuously							
Atezolizumab Administration ^h		X	X	X	X	Every 3 weeks			
Correlative Blood Sample Collection ^{il}	X				X	Every 9 Weeks ^p	X		
Correlative Tumor Biopsy ^{jl}	X				X		X		
Study Treatment Compliance	X	X	X	X	X	Every 3 Weeks	X		
Survival follow-up							X	X	X ^k
Concomitant Medications ^u	Continuously Monitored								
Adverse Events ^v		Continuously Monitored							

^a Chemistry panel includes albumin, ALP, amylase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, GGT, glucose, LDH, lipase, magnesium, phosphorous, potassium, sodium, total bilirubin, and total protein.

^b TFTs include TSH, free T3, and free T4.

^c Serum pregnancy test at baseline only for women of child-bearing potential (WOCBP).

^d Tumor assessments should continue on the protocol-defined schedule, relative to the date of first dose of study treatment, regardless of whether study treatment is given, reduced, held or discontinued. The same imaging modalities used at screening will be used for subsequent tumor assessments after first dose. All sites of known disease must be assessed.

^e MRI with and without contrast is preferred for tumor assessment, but CT is also acceptable in cases where an MRI cannot be scheduled within protocol-defined windows.

^f Response will be evaluated upon the completion of the 3rd cycle (End of Week 9) and every 9 weeks thereafter until end of treatment or disease progression.

^g Cabozantinib treatment will be taken orally at a dose of 40mg/day beginning with Day 1 of Cycle 1 until the end of treatment or disease progression.

^h The initial dose of atezolizumab will be delivered over 60 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

ⁱ Blood samples for correlatives will be collected at baseline, W10 D1, W13 D1, and every 3 cycles (9 weeks) thereafter until disease progression. An additional sample will be collected at the end of treatment visit.

^j Patients will undergo a fresh tissue biopsy at baseline. If it is not possible to collect a fresh biopsy at baseline, archival tissue will be used for research analysis. Additionally, biopsies will be performed after 3 cycles (9 weeks) as deemed medically safe/feasible and an optional biopsy upon disease progression.

^k After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent, or the Investigator terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

^l To be performed/collected within 28 days of Week 1 Day 1 (W1D1).

^m To be performed/collected within 14 days of Week 1 Day 1 (W1D1).

ⁿ +/- 3 calendar day window.

^o The end of treatment and 30 day follow up assessments can be collected on the same day if applicable.

^p +/- 7 calendar day window.

^q +/- 14 day calendar window.

^r For women under the age of 55 years to confirm menopause as needed.

^s Single, local 12-lead ECG. If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

^t Heart rate (HR), Respiratory Rate (RR), Oxygen Saturation (SPO2), Blood pressure (after resting recumbent for >5 minutes) Refer to table 1 for vital sign collection in reference to infusion.

^u Concomitant medications will be recorded starting 7 days prior to initiation of study treatment until the end of treatment visit.

^v After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After the end of the reporting period for serious adverse events and adverse events of special interest, all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up CRF.

^w All assessments will be collected at 30 days after the final dose of study treatment or before initiation of new systemic anti-cancer therapy, whichever occurs first.

27. ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical 'Oncology
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CTLs	Cytotoxic T Lymphocytes
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factors
G-MDSCs	Granulocytic Myeloid-Derived Suppressor Cells
GCP	Good Clinical Practice

GI	Gastrointestinal
HGF	Hepatocyte Growth Factor
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion Related Reactions
LMWH	Low Molecular Weight Heparin
M-MDSCs	Mononuclear Myeloid-Derived Suppressor Cells
mOS	Median Overall Survival
mPFS	Median Progression Free Survival
MTC	Medullary Thyroid Cancer
ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death- 1
PD-L1	Programmed Death Ligand -1
PDAC	Pancreatic Ductal Adenocarcinoma
PE	Pulmonary Embolism
PEG	Percutaneous Endoscopic Gastrostomy
PFS	Progression Free Survival
PDO	Patient Derived Organoid
PPI	Proton Pump Inhibitor
PR	Partial Response
QA/QC	Quality Assurance/Quality Control
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors

RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SRC	Scientific Review Committee
TIA	Transient Ischemic Attack
UACC	University of Arizona Cancer Center
ULN	Upper Limit of Normal
UPCR	Urine Protein/Creatinine Ratio
VEGFR	Vascular Endothelial Growth Factor Receptor

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29. APPENDICES

Appendix I: Guidelines to Managing AEs Related to Cabozantinib

Appendix II: Guidelines to Managing AEs Related to Atezolizumab

Appendix III: Preexisting Autoimmune Diseases and Immune Deficiencies

Appendix IV: Anaphylaxis Precautions

Appendix V: Genentech Safety Reporting Fax Cover Sheet

Appendix I: Guidelines for Managing Cabozantinib Related Adverse Events

Guidelines for Management of Potential Adverse Events Associated with Cabozantinib Treatment

Subjects will be monitored for AEs from the time of signing informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the Investigator. AE severity will be graded by the Investigator in accordance with CTCAE v.5.0.

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

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

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

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

Many AEs can occur early (within the first few weeks) in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting. In addition, earlier onset for events of dehydration was observed in subjects with CRPC when compared with subjects with other tumor types.

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, arterial aneurysm, nephrotic syndrome, hypertension with life-threatening consequences, persistent uncontrolled hypertension despite optimal medical management, rhabdomyolysis, and reversible posterior leukoencephalopathy syndrome (RPLS).

A population pharmacokinetics analysis of cancer subjects with RCC, HCC, MTC, glioblastoma, and other solid tumors predicted a terminal half-life of approximately 99 h for cabozantinib when administered as repeated once-daily doses. Thus, as described above, it will take most subjects 2 to 3 weeks (5 half-lives) to reach steady state with daily dosing after initiating therapy with cabozantinib. AEs attributable to cabozantinib may be expected to occur by the time maximum plasma concentrations are reached, and therefore early intervention with dose modifications within the first 15-21 days of daily dosing may be justified.

Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess:

Prior to initiation of treatment with cabozantinib, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Tumors invading GI or respiratory tracts.
- Active peptic ulcer disease, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis.
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.
- Ongoing visceral complications from prior radiation therapy.
- Prior GI surgery (particularly when associated with delayed or incomplete healing).

Complete healing following abdominal surgery and radiation therapy and/or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

After starting 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. 2008) 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 below. 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.

Management of Diarrhea Associated with Cabozantinib

Event	Management
Tolerable Grade 1-2 (duration < 48 h)	- Continue with study treatment and consider dose reduction. - Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). - Dietary modifications (e.g., small lactose-free meals, bananas and rice). - Intake of isotonic fluids (1-1.5 L/day). - Re-assess after 24 hours: - Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval. - Diarrhea not resolving: Continue/resume antidiarrheal treatment.
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	- Interrupt study treatment. - Ask subject to attend clinic. - Rule out infection (e.g., stool sample for culture). - 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. - Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose. - Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist.

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 7 for further details).

Non-Gastrointestinal Fistula

Radiation therapy (in certain areas of the body) has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (e.g., radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib until these complications have resolved.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 4 weeks of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. 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 evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

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

The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Though the incidence of CNS hemorrhage events in a study of subjects with glioblastoma was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of hemorrhage in glioblastoma translates to a risk of hemorrhage for subjects with brain metastases. Currently, treated brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion for symptoms that could be due to a CNS hemorrhage occur.

Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment, and cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

Vascular Disorders

Thromboembolic Events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued. See Section 7.2 for additional restrictions on anticoagulation therapy.

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

The available cabozantinib data from clinical studies and postmarketing experience showed that arterial aneurysms and dissections may occur rarely during cabozantinib treatment. These events appear to primarily occur in the presence of hypertension (which is a known risk factor for this condition); however, in some events the presence of hypertension was not documented. Discontinuation of treatment with cabozantinib should be considered in subjects who develop aortic aneurysm and dissections.

Hypertension

The below table provides treatment guidelines for hypertension deemed related to cabozantinib. Subjects with known hypertension should be optimally managed prior to entry into clinical trials with cabozantinib according to entry criteria of specific protocols. 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 hypertension with life-threatening consequences or when urgent intervention is indicated, and appropriate medical management should be initiated.

Management of Hypertension Associated with Cabozantinib

Event	Management
Subjects NOT receiving optimized antihypertensive therapy	
≥ 140 mm Hg (systolic) ^a and < 160 mm Hg OR ≥ 90 mm Hg (diastolic) and < 100 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, treatment should be interrupted and can only be restarted once symptoms have resolved and BP is < 140 mm Hg systolic and < 90 mm Hg diastolic
≥ 160 mm Hg (systolic) OR ≥ 100 mm Hg (diastolic)	- Reduce cabozantinib by one dose level^b or interrupt cabozantinib treatment per Investigator discretion. 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 > 100 mm Hg, or if subject is symptomatic - Add new or additional antihypertensive 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 < 160 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted - Restart cabozantinib treatment at the reduced dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic
Hypertension with life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	- Discontinue cabozantinib treatment - Initiate appropriate medical management
^a Guidance based on CTCAE v5.	
^b Permitted dose levels are defined by individual protocols.	

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

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

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

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

Event	Management
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. ^a Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if 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 PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if 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 cabozantinib at a reduced dose if PPES recovers to Grade ≤ 1 . Discontinue subject from cabozantinib if PPES does not improve within 6 weeks.
^a Permitted dose levels are defined by individual protocols.	

Angioedema

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

Osteonecrosis

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

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

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

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 3 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Withhold cabozantinib for development of ONJ until complete resolution.

Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. The below table 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).

Management of Proteinuria Associated with Cabozantinib

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

Nervous System Disorders

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

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

Hepatocellular Toxicity

Investigators should monitor for DILI diligently and report any potential events. Elevation of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevations of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other potential causes for these increases (e.g., cancer-related, infection) should be evaluated.

Management of Hepatocellular Toxicity Associated with Cabozantinib

Event – Elevation of ALT, AST, or Total Bilirubin (CTCAE v5)	Management
Grade 1 ALT or AST > ULN – 3.0 x ULN Bilirubin > ULN – 1.5 x ULN	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2 ^{a,b} ALT or AST > 3.0 – 5.0 x ULN Bilirubin > 1.5 – 3.0 x ULN	• Interrupt cabozantinib if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart cabozantinib after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade 3 ^{a,b} ALT or AST > 5.0 – 20.0 x ULN Bilirubin > 3.0 – 10.0 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 at least CTCAE Grade ≤ 1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment.
Grade 4 ^b ALT or AST > 20.0 x ULN Bilirubin > 10 x ULN	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator and approved by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.
^a 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. ^b The following condition requires discontinuation of cabozantinib: Drug-related ALT or AST >3 x ULN in combination with total bilirubin >2 x ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).	

Infections and Infestations

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

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

Blood and Lymphatic System Disorders

Hematological toxicities (i.e., neutropenia, thrombocytopenia, and anemia) 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 unless inhibited by protocol. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Fatigue

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

Weight Loss

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

Corrected QT Prolongation

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

Unless otherwise specified, only subjects with a baseline QTcF $\leq$ 500 msec are eligible for cabozantinib research studies. Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or drugs known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment.
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management.
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (<http://www.qtdrugs.org>).
- Repeat ECG triplicates hourly until the average QTcF is $\leq$ 500 ms and the average increase is $\leq$ 60 ms above baseline, 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.
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to $\leq$ 500 ms or return to $\leq$ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved.
- Principal Investigator 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.

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. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported, but a causal association has not been established. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and approved by the Principal Investigator. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

Electrolyte Abnormalities

Electrolyte abnormalities, including hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia have been noted in subjects treated with cabozantinib. In some cases, these have been Grade 3 or 4 and/or serious. Electrolyte values should be evaluated routinely. Deficits should be corrected when an electrolyte abnormality is noted in order to avoid worsening. Correction of electrolyte abnormalities should be accompanied by increased frequency of monitoring.

Appendix II: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator.

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea fatigue, hypoxia, pneumonitis, and pulmonary. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in [Table 1](#).

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. • Consider resuming on radiographic evidence of improvement.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to pulmonary and infectious disease specialist and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^{c, d} • For recurrent events or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab.^c • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL is recommended with or without transbronchial biopsy. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

^d In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout atezolizumab treatment. Management guidelines for hepatic events are provided in [Table 2](#).

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	- Continue atezolizumab. - Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	All events: - Monitor LFTs more frequently until return to baseline values. Events of ≥ 5 days' duration: - Withhold atezolizumab for up to 12 weeks after event onset.^a - Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c
Hepatic event, Grade 3 or 4	- Permanently discontinue atezolizumab.^c - Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. - Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI=gastrointestinal; HCC = hepatocellular carcinoma; LFT = liver function test; ULN=upper limit of normal.

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in [Table 3](#).

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with 1-2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i> • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c

Table 4 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab.^c • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
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GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in [Table 4](#).

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 5 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 Hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patients to the hospital for developing myxedema (bradycardia, hypothermia and altered mental status). • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab.^c
Grade 1 hyperthyroidism	TSH $\geq$ 0.1 mU/L and $<$ 0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. TSH $<$ 0.1 mU/L: • Follow guidelines for <i>Grade 2</i> hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab.^c
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.^b • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab.^c
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin if needed. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve, and glucose levels are stable.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab.^c • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in [Table 5](#).

Table 6 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	- Continue atezolizumab. - Patient referral to ophthalmologist is strongly recommended. - Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. - If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Patient referral to ophthalmologist is strongly recommended. - Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c
Ocular event, Grade 3 or 4	- Permanently discontinue atezolizumab.^c - Refer patient to ophthalmologist. - Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis

resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 6](#).

Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis.

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 7 Management Guidelines for Immune-Mediated Cardiac Events

Events	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction ([Lee et al. 2019](#)). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-L1 or PD-1 ([Rotz et al. 2017](#); [Adashek and Feldman 2019](#)), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in [Table 7](#).

Severe SARS-COV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon- γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per the investigator's judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 8 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 ^a Fever ^b with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, ^c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (≥ 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 ^a Fever ^b with hypotension not requiring vasopressors <u>and/or</u> Hypoxia requiring low-flow oxygen ^d by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. ^c • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the investigator.

Table 9 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Grade 3 ^a Fever ^b with hypotension requiring a vasopressor (with or without vasopressin) <u>and/or</u> Hypoxia requiring high-flow oxygen ^d by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab. ^e • Administer symptomatic treatment. ^c • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4 ^a Fever ^b with hypotension requiring multiple vasopressors (excluding vasopressin) <u>and/or</u> Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab. ^e • Administer symptomatic treatment. ^c • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments ^f may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

- ^a Grading system for management guidelines is based on ASTCT consensus grading Scale for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
- ^b Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
- ^c Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
- ^d Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
- ^e Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.
- ^f Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in [Table 8](#).

Table 10 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase > 1.5-2.0×ULN: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase > 2.0-5.0×ULN: • Treat as Grade 3.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c • For recurrent events, permanently discontinue atezolizumab.^c

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c • For recurrent events, permanently discontinue atezolizumab.^c
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab.^c • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

DERMATOLOGIC EVENTS

The majority of cases of rash [reported with the use of atezolizumab](#) were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in [Table 9](#).

Table 11 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	- Continue atezolizumab. - Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	- Continue atezolizumab. - Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. - Initiate treatment with topical corticosteroids. - Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	- Withhold atezolizumab for up to 12 weeks after event onset. ^a - Refer patient to dermatologist for evaluation and, if indicated, biopsy. - Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. - If event resolves to Grade 1 or better, resume atezolizumab. ^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. ^c
Dermatologic event, Grade 4	Permanently discontinue atezolizumab. ^c
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: - Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. - Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. - Follow the applicable treatment and management guidelines above. - If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in [Table 10](#), with specific guidelines for myelitis provided in [Table 11](#).

Table 12 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	- Continue atezolizumab. - Investigate etiology. - Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-related neuropathy, including facial paresis, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Investigate etiology and refer patient to neurologist. - Initiate treatment as per institutional guidelines. - For general immune-mediated neuropathy: - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c - For facial paresis: - If event resolves fully, resume atezolizumab.^b - If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab.^c
Immune-related neuropathy, including facial paresis, Grade 3 or 4	- Permanently discontinue atezolizumab.^c - Refer patient to neurologist. - Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	- Permanently discontinue atezolizumab. - Refer patient to neurologist. - Initiate treatment as per institutional guidelines. - Consider initiation of 1-2 mg/kg/day oral or IV prednisone or equivalent.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

Table 11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	- Continue atezolizumab unless symptoms worsen or do not improve. - Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	- Permanently discontinue atezolizumab. - Investigate etiology and refer patient to a neurologist. - Rule out infection. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	- Permanently discontinue atezolizumab. - Refer patient to a neurologist. - Initiate treatment as per institutional guidelines.

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 12](#).

Table 12 Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab.. • Refer patient to neurologist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

RENAL EVENTS

Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout atezolizumab treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 13](#).

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	- Continue atezolizumab. - Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset. ^a - Refer patient to renal specialist. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better, resume atezolizumab. ^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. ^c
Renal event, Grade 3 or 4	- Permanently discontinue atezolizumab. - Refer patient to renal specialist and consider renal biopsy. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 14](#).

Table 14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	- Continue atezolizumab. - Refer patient to rheumatologist or neurologist. - Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Refer patient to rheumatologist or neurologist. - Initiate treatment as per institutional guidelines. - Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c
Immune-mediated myositis, Grade 3	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Refer patient to rheumatologist or neurologist. - Initiate treatment as per institutional guidelines. - Respiratory support may be required in more severe cases. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.^c - For recurrent events, treat as Grade 4 event. Permanently discontinue atezolizumab.^c
Immune-mediated myositis, Grade 4	- Permanently discontinue atezolizumab.^c - Refer patient to rheumatologist or neurologist. - Initiate treatment as per institutional guidelines. - Respiratory support may be required in more severe cases. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator.
 - ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
 - ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit- risk assessment and documented by the investigator.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq 38.5^{\circ}\text{C}$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
 - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
 - Platelet count $< 100 \times 10^9/\text{L}$ (100,000/ μL)
 - ANC $< 1.0 \times 10^9/\text{L}$ (1000/ μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
 - Platelet count $\leq 181 \times 10^9/\text{L}$ (181,000/ μL)
 - AST ≥ 48 U/L
 - Triglycerides > 1.761 mmol/L (156 mg/dL)
 - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in [Table 15](#).

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; IV = intravenous; MAS = macrophage activation syndrome.

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APPENDIX III: Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis).

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves' disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthrits • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis
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APPENDIX IV: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

Stop the study treatment infusion.

Call for additional medical assistance.

Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.

Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.

Continue to observe the participant and document observations.

Draw serum/plasma samples for immunogenicity testing.

Ask participant to return for washout immunogenicity sample if appropriate.

APPENDIX V: Genentech Safety Reporting Fax Cover Sheet



SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[] - [] - []
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SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET