EXELIXIS®

CLINICAL STUDY PROTOCOL

A Randomized, Controlled Phase 3 Study of Cabozantinib (XL184) in Combination with Atezolizumab versus Sorafenib in Subjects with Advanced Hepatocellular Carcinoma Who Have Not Received Previous Systemic Anticancer Therapy

PROTOCOL NUMBER:	XL184–312
STUDY TREATMENT:	Cabozantinib in Combination with Atezolizumab vs Sorafenib
IND NUMBER:	140,189
EudraCT NUMBER:	2018-003354-24
SPONSOR:	Exelixis, Inc. 1851 Harbor Bay Parkway Alameda, CA 94502
MEDICAL MONITOR:	PPD
DATE FINAL (Version 0.0):	31 August 2018
DATE AMENDED:	12 April 2019 **PROTOCOL AMENDMENT 1.0**
	09 April 2020 **PROTOCOL AMENDMENT 2.0**
	14 May 2021 **PROTOCOL AMENDMENT 3.0**
	28 March 2022 **PROTOCOL AMENDMENT 4.0**
	24 January 2023 **PROTOCOL AMENDMENT 5.0**

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PROTOCOL APPROVAL PAGE

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INVESTIGATOR SIGNATURE PAGE

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By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol or protocol amendment referenced above.

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

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PROTOCOL NUMBER

XL184-312

CLINICAL PHASE

Phase 3

RATIONALE

Liver cancer is the second most frequent cause of cancer deaths worldwide (Ferlay et al 2015). Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 90% of cases. In 2015, 854,000 new liver cancer cases were reported worldwide and 810,000 deaths occurred (Global Burden of Disease Liver Cancer 2017; EASL 2018). The estimated incidence and mortality rates of liver cancer in the USA in 2016 were approximately 42,000 and 30,000 cases, respectively (American Cancer Society 2018); incidence and mortality in the EU in 2012 were 52,000 and 48,000 cases, respectively (Ferlay et al 2013).

Surgical resection and transplantation are potential curative treatment modalities for HCC. Ablative therapies (eg, radiofrequency ablation [RFA], microwave ablation [MWA], and percutaneous ethanol injection [PEI]) are being used for early stage unresectable HCC. Transarterial chemoembolization (TACE) is used generally for intermediate stage disease. The current standard of care for first line treatment of advanced unresectable HCC is sorafenib, which is a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases. In a randomized placebo-controlled Phase 3 study (SHARP), sorafenib improved the primary endpoint of overall survival (OS) in subjects with advanced HCC (Child-Pugh A) who had not received prior systemic therapy (Llovet et al 2008). Median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.55, 0.87; p-value < 0.001). A similar HR was observed (with a shorter duration of OS than in the SHARP trial) in a corresponding placebo-controlled Phase 3 trial conducted in an Asian-Pacific population in which infection with hepatitis B virus (HBV) was the main cause of HCC: median OS was 6.5 months vs 4.2 months (HR 0.68; 95% CI: 0.50, 0.93; p-value = 0.014) (Cheng et al 2009). Recently, the VEGFR-targeting tyrosine kinase inhibitor (TKI) lenvatinib was shown to be non-inferior to sorafenib in a Phase 3 study enrolling subjects with advanced HCC who had not received prior systemic therapy (Kudo et al 2018) leading to US and EU approval in this population. In that study, median OS for lenvatinib was 13.6 months compared with 12.3 months for sorafenib (HR 0.92; 95% CI 0.79, 1.06).

Cabozantinib is an orally bioavailable small molecule TKI that potently inhibits VEGFR, MET, AXL, and RET, as well as a number of other receptor tyrosine kinases (RTKs) that have also been implicated in tumor pathobiology, including KIT and FLT3. Cabozantinib suppresses MET

and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. 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 prescribing information [US PI] and European Medicines Agency Summary of Product Characteristics [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). Based on the results from the studies below, cabozantinib tablets (60 mg) as a single agent have also been approved in the US and EU for the treatment of HCC in patients who have previously been treated with sorafenib (Cabometyx US PI and EMA SmPC).

The clinical activity and safety of single agent cabozantinib (60 mg, tablets) in HCC has been demonstrated in a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects who had received prior therapy with sorafenib (subjects were required to have progressed during or following prior systemic therapy and up to 2 prior lines of systemic therapy were allowed; Abou-Alfa et al 2018). The primary endpoint of the study was OS. At the second pre-planned interim analysis, the prespecified event-driven primary efficacy endpoint analysis of the 707 subjects enrolled at the data cutoff (470 cabozantinib, 237 placebo) demonstrated a statistically significant improvement in OS for subjects in the cabozantinib arm compared with placebo (Intent-to-Treat [ITT] population): the HR, adjusted for stratification factors, was 0.76 (95% CI 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value to reject the null hypothesis of equal OS = 0.021). The Kaplan-Meier estimates for median duration of OS were 10.2 months in the cabozantinib arm vs 8.0 months in the placebo arm. The secondary endpoint analysis of progression-free survival (PFS) as determined by the investigator yielded a median duration of PFS of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors, was 0.44 (95% CI 0.36, 0.52, stratified log-rank p-value < 0.0001). Investigator-determined objective response rate (ORR) was 4% and 0.4% for subjects in the cabozantinib and placebo arms, respectively (unstratified Fisher exact test p-value = 0.0059); all were partial responses (PRs). In addition, there was a high rate of stable disease (SD) in the cabozantinib arm relative to placebo (60% vs 33%). Adverse events reported for ≥ 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), fatigue, nausea, hypertension, vomiting, aspartate aminotransferase (AST) increased, and asthenia. Grade 3 or 4 adverse events (AEs) regardless of causality were reported for 68% of subjects in the cabozantinib arm and 36% in the placebo arm. Grade 3 or 4 AEs reported for ≥ 5% of subjects in the cabozantinib arm by decreasing frequency were PPE, hypertension, AST increased, fatigue, diarrhea, asthenia, and decreased appetite. The results of this study formed the basis for regulatory applications to the US FDA and EMA to approve cabozantinib for treatment of patients with advanced HCC who have received prior therapy. Earlier clinical evaluation of cabozantinib in HCC was conducted in a Phase 2 study that included both previously-treated and treatment-naïve subjects with advanced HCC (n=41; Kelley et al 2017). Progression-free survival from first dose throughout the study was estimated for all HCC subjects using a piecewise method; median PFS was 5.2 months. Tumor regression appeared independent of prior sorafenib exposure.

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody which potently and selectively inhibits binding of programmed death ligand 1 (PD-L1) on tumor cells and tumor infiltrating immune cells in the tumor microenvironment (McDermott et al 2016). Through this interaction, atezolizumab interrupts the negative regulatory effects of PD-L1 on T-cell proliferation and function that result from PD-L1 binding to programmed death receptor 1 (PD-1) and B7.1 (CD80) expressed on T lymphocytes and other immune cells. The result is an increase in the susceptibility of tumor cells to T-cell-mediated immune response, an effect that has been demonstrated in clinical activity across several tumor types.

Atezolizumab injection, for intravenous (IV) use (1200 mg once every 3 weeks [q3w]), has been approved in the United States and the European Union for the treatment of patients with advanced urothelial carcinoma (UC) after prior platinum containing chemotherapy or in a subset patients who are considered cisplatin-ineligible (different patient populations are indicated depending on region; Rosenberg et al 2016, Balar et al 2017). Atezolizumab is also approved for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy (Fehrenbacher et al 2016; Tecentriq™ US PI and EMA SmPC). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). Treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs).

The clinical activity and safety of atezolizumab has been evaluated in subjects with advanced HCC either as single agent or in combination therapy. In a Phase 1b study of atezolizumab (1200 mg q3w) in combination with the anti-VEGF targeting antibody bevacizumab, 103 subjects with advanced HCC naïve to systemic therapy had been enrolled at the data cutoff of 26 July 2018 (NCT02715531; Pishvaian et al 2018). Among 73 efficacy-evaluable subjects, the median survival follow-up was 7.2 months. The ORR by independent radiology facility (IRF) was 27% (with 4 complete responses [CRs]) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and was 34% (with 8 CRs) per modified RECIST (mRECIST); ORR by Investigator per RECIST 1.1 was 32% with 1 CR. Confirmed responses were reported across the patient population regardless of HCC etiology, geographic region, baseline alpha-fetoprotein (AFP) levels, or extrahepatic spread of tumor. The investigator-assessed median PFS per RECIST 1.1 was 14.9 months, and the IRF-assessed median PFS per RECIST 1.1 was 7.5 months. Median estimates for duration of response (DOR) and OS were not yet reached at the data cutoff of 26 July 2018. Among the 103 safety evaluable subjects, treatment-related Grade 3 or 4 AEs were reported in 28 subjects (27%), most commonly hypertension (n = 10 [10%]). Five (5) Grade 5 AEs were observed, 2 of which were assessed as treatment related (one sepsis, one pneumonitis). A total of 19 subjects (18%) experienced treatment-related serious adverse events (SAEs). Adverse events of special interest (AESIs) of any grade for atezolizumab were reported for 54% of subjects, and AESIs of any grade for bevacizumab were reported for 47% of subjects. Immune-related AESIs for atezolizumab of ≥ Grade 3 requiring corticosteroid treatment included pneumonitis (2 subjects), autoimmune encephalitis, drug-induced liver injury (DILI), colitis, AST increased, γ-glutamyltranspeptidase (GGT) increased, diabetes mellitus, and pancreatitis (1 subject each). The high response rate observed suggested that the combination of atezolizumab

with bevacizumab has synergistic activity in advanced HCC and compared favorably to early single-agent atezolizumab data in treatment-naïve HCC. Limited information is currently available for atezolizumab as a single agent in patients with advanced HCC. A total of 12 subjects were enrolled in two Phase 1 studies. In these two studies, few responses were observed: one study with 5 subjects had no responses (NCT01375842), and one study with 7 subjects had two confirmed responses per investigator assessment (NCT02825940).

Targets of cabozantinib are also implicated in promoting tumor immune suppression including TYRO3, MER, and AXL (TAM family kinases). Preclinical studies (Kwilas et al 2014, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment that may present an opportunity for synergistic effects from combined treatment with immune checkpoint inhibitors (ICIs). A Phase 1b study (NCT03170960) is currently evaluating the combination of cabozantinib with atezolizumab in multiple tumor cohorts. In the dose escalation stage of the study, cabozantinib dose levels of 40 mg and 60 mg once daily (qd) were evaluated in 6 subjects each (atezolizumab was administered at 1200 mg IV q3w for all subjects). At both cabozantinib dose levels in the dose-limiting toxicity (DLT) evaluation period of the dose escalation stage of the study there were no DLTs or SAEs (n=12 subjects total). The majority of AEs were of Grade 1 or 2 including irAEs. Grade 3 AEs included five events of hypertension, two events each of diarrhea and hypophosphatemia, and one event each of pulmonary embolism, hyperglycemia, GGT increased, AST increased, ALT increased, lymphocyte count decreased, lipase increased, muscular weakness, nephritis, and myositis (verbatim term). No Grade 4 or 5 AEs were reported. Among 10 subjects with clear cell RCC enrolled in the dose escalation stage, the investigator-assessed confirmed ORR was 70% with 1 CR and 6 PRs. Cabozantinib 40 mg in combination with atezolizumab 1200 mg was selected as the recommended dose for the Expansion Stage cohorts because of its favorable safety profile over a prolonged time on study treatment with minimal dose reductions and encouraging preliminary efficacy, which was deemed to optimize the benefit/risk of the combination. The study is ongoing and currently enrolling expansion cohorts in multiple solid tumor types including subjects with advanced HCC who have not received prior systemic anticancer therapy. As of 05 February 2019, 157 additional subjects had been enrolled in the expansion cohorts evaluating cabozantinib (40 mg, qd) + atezolizumab (1200 mg IV q3w); information on the 141 subjects evaluable for safety as of 29 January 2019 is provided in Section 1.4.

Targeting the VEGF signaling pathway with small molecule TKIs has improved the clinical outcome of patients with advanced HCC; however, the OS has been modest with a median OS between 10.7 and 13.6 months (SHARP trial, Llovet et al 2008; REFLECT trial, Kudo et al 2018). More recently ICI therapies are being evaluated as potential new treatment strategy in HCC. Both cabozantinib and atezolizumab have shown encouraging clinical activity in advanced HCC. Based on the potential synergistic effects the combination of cabozantinib with atezolizumab appears to be a promising treatment opportunity for subjects with advanced HCC. Therefore, further evaluation of cabozantinib in combination with atezolizumab in subjects with previously untreated advanced HCC is warranted.

This Phase 3 study evaluates the safety and efficacy of cabozantinib in combination with atezolizumab (approximately 370 subjects) versus the standard of care sorafenib (approximately 185 subjects) in subjects with advanced HCC who have not received previous systemic anticancer therapy. A single-agent cabozantinib arm (approximately 185 subjects) will be enrolled in which

subjects will receive single-agent cabozantinib in order to determine its contribution to the overall safety and efficacy of the combination with atezolizumab in this patient population.

It is planned to include up to 148 subjects from mainland China in this study to assess safety and efficacy in the China subpopulation. In the event enrollment in mainland China is incomplete by the time the global enrollment phase has been completed, a Mainland China Extension Phase will be implemented to complete enrollment and facilitate subpopulation analyses as needed. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).

XL184-312 Protocol Amendment 2.0 introduced considerations and study-related measures necessary due to the COVID-19 pandemic. XL184-312 Protocol Amendment 3.0 expanded the COVID-19-related guidance to include instructions for managing subjects who become infected on study, considerations for administration of COVID-19 vaccines, and confirmation that the COVID-19 accommodations are temporary and will be repealed back to standard study conduct when conditions allow.

OBJECTIVES

The primary objective of this study is to evaluate the efficacy of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. A secondary objective is to evaluate the activity of single-agent cabozantinib compared with sorafenib in this patient population.

Primary efficacy endpoints:

- Duration of PFS per RECIST 1.1, by Blinded Independent Radiology Committee (BIRC) for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib)
- Duration of OS for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib)

Secondary efficacy endpoint:

- PFS per RECIST 1.1 by BIRC for the single-agent cabozantinib arm vs the control arm (sorafenib)

Additional endpoints:

- ORR, time to progression (TTP), and DOR per RECIST 1.1 by BIRC and Investigator
- Evaluation of radiographic response per modified RECIST (mRECIST)
- Safety through the evaluation of AEs, including irAEs and other AESIs.
- Characterization of the pharmacokinetics (PK) of cabozantinib in subjects with previously untreated HCC
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Change in serum AFP from baseline
- Correlation of biomarker analyses with clinical outcomes

- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)
- Healthcare resource utilization

STUDY DESIGN

This is a multicenter, randomized, open-label, controlled Phase 3 trial of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. The multiple primary efficacy endpoints are PFS and OS for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib). Additionally there will be a third arm to evaluate the safety and clinical activity of single-agent cabozantinib. Approximately 740 eligible subjects with advanced HCC were planned to be randomized in a 2:1:1 ratio at approximately 250 sites in this trial in the global enrollment phase of the study. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects. After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. If initiated, subjects recruited in the Mainland China Extension Phase will be randomized according to the same 2:1:1 scheme as subjects in the global enrollment phase. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).

The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined. The Mainland China Extension Phase will not be expanded beyond 148 subjects.

Special accommodations during the global COVID-19 pandemic are described in Appendix M.

The trial consists of the following phases:

Pre-Treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Guidance for diagnosis of HCC in cirrhotic patients by imaging is provided in Section 5.8.6.1.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1:1 manner to receive study treatment as follows:

Experimental arm (at least 370 subjects):
cabozantinib (40 mg oral, qd) +
atezolizumab (1200 mg infusion, q3w)

Control arm (at least 185 subjects):
sorafenib (400 mg, twice a day [bid])

Single-Agent Cabozantinib Arm (approximately 185 subjects):
cabozantinib (60 mg qd)

Randomization will be stratified by the following factors established at screening:

- Disease etiology (HBV [with or without hepatitis C virus {HCV}], HCV [without HBV], or Other)
- Region (Asia, Other)
- Presence of extrahepatic disease and/or macrovascular invasion (Yes, No)

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until there is unacceptable toxicity, the need for subsequent systemic anticancer treatment, or any other reasons for the treatment discontinuation listed in the protocol. Treatment may continue after radiographic progression per RECIST 1.1 according to the criteria outlined in Section 5.8.6.3. Subjects on the experimental arm (cabozantinib and atezolizumab) are allowed to discontinue one component of the study treatment but continue to receive the other. Escalation of cabozantinib from 40 mg qd to 60 mg qd in the experimental arm is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd. Crossover from the control to experimental therapy will not be allowed unless study transitions to a Crossover Phase (see below).

Crossover Phase: The study may transition to a Crossover Phase if the analysis of the multiple primary endpoint of OS for the global ITT population (ie, not including subjects enrolled in the Mainland China Extension Phase) shows statistically significant and clinically meaningful evidence of improvement.

The Crossover Phase will only be implemented upon decision by the Sponsor and following any required discussion with regulatory authorities following review of the data. Crossover may be implemented independently and at different points in time for study sites and subjects in mainland China compared to other sites and subjects in the global study. If the decision is made to enter the Crossover Phase, study sites will have 8 weeks to determine eligibility and begin administration of crossover treatment (cabozantinib + atezolizumab combination) to eligible subjects randomized to the control arm (sorafenib) or the single-agent cabozantinib arm; subsequently no further crossover will be allowed.

- Subjects randomized to the sorafenib control arm or the single-agent cabozantinib arm will have the option to cross over to receive the cabozantinib + atezolizumab combination if they meet predefined eligibility criteria.
- Subjects randomized to the cabozantinib + atezolizumab experimental arm who are still receiving study treatment and subjects randomized to the sorafenib control arm or the single-agent cabozantinib arm who are still receiving study treatment and do not cross over to the combination treatment (cabozantinib + atezolizumab) may continue on their originally assigned study treatment until a criterion for protocol-defined discontinuation has been met.

- Subjects randomized to the cabozantinib + atezolizumab experimental arm who are in the Post-Treatment Period and subjects randomized to the sorafenib control arm or the single-agent cabozantinib arm who do not cross over to cabozantinib + atezolizumab and are in the Post-Treatment Period will continue with post treatment assessments.

The study is expected to have completed enrollment in the global enrollment phase at the time of transitioning to the Crossover Phase for those subjects, but accrual of subjects in the Mainland China Extension Phase may still be ongoing at that point. In the Crossover Phase safety assessments and efficacy assessments will be performed per the schedule of assessments. PK, biomarker, health-related quality of life (HRQOL), and healthcare resource utilization assessments will be discontinued.

Post-Treatment Period: A first Post-Treatment Follow-up visit (FU-1) for safety evaluation (including subjects in the Maintenance Phase [below]) is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second Post-Treatment Follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix K.

Radiographic tumor and HRQOL assessments are to continue, regardless of whether study treatment is given, reduced, held, or discontinued until a protocol-defined criterion for ending radiographic assessments is met (see Section 5.8.6.2). Consequently these assessments may be required in the Post-Treatment Follow-up Period for some subjects.

In addition, subjects are to be contacted every 12 weeks (± 14 days) after FU-2 to assess survival status and document receipt of subsequent anticancer therapy. This follow-up will continue until the subject expires or the Sponsor decides to discontinue collection of these data; however, these assessments are not required in the Maintenance Phase (below). Every effort must be made to perform these evaluations unless consent for non-interventional study assessment is withdrawn.

Mainland China Extension Phase: After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. The Pre-Treatment, Treatment, and Post-Treatment Periods of the study will be conducted in the same manner in the Mainland China Extension Phase as for subjects who were enrolled in the global enrollment phase.

Study Completion: The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS (experimental vs control arm) in either of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results), all other planned formal inference tests have been performed (eg, for secondary efficacy endpoints), and any required supportive analyses for China are completed.

Maintenance Phase/Treatment after Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, subjects who continue study treatment may enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental

treatment regimen within this study to have been sufficiently established and data analyses required for regulatory purposes to have been completed. If a Crossover Phase has been implemented, the Maintenance Phase may not begin before the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last subject randomized to sorafenib or single-agent cabozantinib who crossed over to receive cabozantinib + atezolizumab. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects will continue to receive study treatment until they meet the protocol-required criteria for treatment discontinuation. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments. The nature and frequency of these assessments during the Maintenance phase are to be performed per institutional standard of care and guidance from the Sponsor. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of SAEs; certain AEs (including irAEs and other AESIs [whether serious or not], and AEs leading to dose modifications or treatment discontinuation); and other reportable events (DILI, pregnancy, and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

The study clinical database will be closed upon initiation of the Maintenance Phase. Important safety information (noted above) collected in the Maintenance Phase will be captured in the safety database. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

End of Trial: End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

NUMBER OF SUBJECTS

Approximately 740 eligible subjects were planned to be randomized 2:1:1 to receive cabozantinib in combination with atezolizumab (n=370), sorafenib (n=185), or single-agent cabozantinib (n=185) in the global enrollment phase of the study. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects.

The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined.

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. The Mainland China Extension Phase will not be expanded beyond 148 subjects. The global population will include all subjects enrolled during the global enrollment phase

(including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).

TARGET POPULATION

To be eligible for the study the subject must meet all of the inclusion and none of the exclusion criteria. The Sponsor will not grant exceptions to these eligibility criteria:

Inclusion Criteria

1. Histological or cytological diagnosis of HCC or clinical diagnosis of HCC in cirrhotic patients by multiphase imaging using CT or MRI per the American Association for the Study of Liver Diseases (AASLD) (Marrero et al 2018) or European Association for the Study of the Liver (EASL 2018) guidelines.

   Note: Sites must receive Sponsor accreditation for imaging-based diagnosis of HCC prior to implementing this methodology. In addition, subjects who do not meet the AASLD or EASL guidelines for imaging diagnosis of HCC or who do not have cirrhosis must have histological or cytological diagnosis of HCC.

2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE).
3. The subject is receiving antiviral therapy per local standard of care if the subject has active HBV infection (defined by HBsAg positive); the subject must have HBV DNA < 500 IU/mL.
4. Measurable disease per RECIST 1.1 as determined by the Investigator.
5. Barcelona Clinic Liver Cancer (BCLC) stage Category B or C (Appendix I).
6. Child-Pugh Score of A (Appendix J).
7. Recovery to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy as determined by the Investigator.
8. Age eighteen years or older on the day of consent.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization:
    a. Absolute neutrophil count (ANC) ≥ 1500/µL (≥ 1.5×10^9/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. White blood cell (WBC) count ≥ 2000/µL (≥ 2.0×10^9/L).
    c. Platelets ≥ 60,000/µL (≥ 60×10^9/L) without transfusion within 2 weeks before screening laboratory sample collection.
    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 2 weeks before screening laboratory sample collection.

e. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)

f. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) ≤ 5 × upper limit of normal (ULN).

g. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L).

h. Serum albumin ≥ 2.8 g/dL (≥ 28 g/L).

i. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 3).

j. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h protein ≤ 1 g.

11. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessment except those procedures performed as standard of care within the screening window.

12. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix H) during the course of the study and for 5 months after the last dose of study treatment. A barrier method (eg, condom) is also required.

13. 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 is 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 hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

Exclusion Criteria

1. Known fibrolamellar carcinoma, sarcomatoid HCC or mixed hepatocellular cholangiocarcinoma.

2. Prior systemic anticancer therapy for advanced HCC including but not limited to chemotherapy, small molecule kinase inhibitors, and ICIs. Subjects who have received local intratumoral or arterial chemotherapy are eligible.

3. Documented hepatic encephalopathy (HE) within 6 months before randomization (see Section 6.6.2.4 for a case definition of HE).

4. Clinically meaningful ascites (ie, ascites requiring paracentesis or escalation in diuretics) within 6 months before randomization.

5. Subjects who have received any local anticancer therapy including surgery, PEI, RFA, MWA, transarterial chemoembolization (TACE), or transarterial radioembolization (TARE) within 28 days prior to randomization

6. Radiation therapy for bone metastasis within 2 weeks, any other external beam radiation therapy within 8 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 8 weeks prior to randomization. Subjects who are neurologically symptomatic or are receiving systemic corticosteroid treatment at the planned time of randomization are not eligible.
8. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:
    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
9. Administration of a live, attenuated vaccine within 30 days prior to randomization.
10. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents.
11. The subject has uncontrolled, significant intercurrent or recent (within the last 3 months before randomization [unless otherwise specified below]) illness including, but not limited to, the following conditions:
    a. Cardiovascular and cardiac disorders:
        i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, 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 (eg, deep vein thrombosis [DVT], pulmonary embolism) within 6 months before randomization.
        iv. History of risk factors for torsades de pointes (eg, long QT syndrome).
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra-abdominal abscess must be confirmed prior to randomization.
        iii. Gastric or esophageal varices that are untreated or incompletely treated with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy

(according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months before randomization are eligible.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major blood vessel, including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the intrahepatic vasculature, including portal vein, hepatic vein, and hepatic artery, are eligible.

f. Other clinically significant disorders such as:

i. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix D for a more comprehensive list of autoimmune diseases and immune deficiencies). Subjects with the following conditions are eligible for the study:

- A history of autoimmune-related hypothyroidism and on thyroid replacement hormone
- Controlled Type 1 diabetes mellitus and on an insulin regimen
- Asthma that requires intermittent use of bronchodilators
- Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true:
    - Rash covers < 10% of body surface area
    - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
    - 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

ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before randomization.
Note: Inhaled, intranasal, intra-articular, and topical corticosteroids and mineralocorticoids are permitted.
Transient use of systemic corticosteroids for allergic conditions such as contrast allergy is allowed.

iii. Active infection requiring systemic treatment, 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. Subjects with active hepatitis B virus infection controlled with antiviral therapy are eligible (see Inclusion Criterion 3). Subjects with active, uncontrolled hepatitis C virus infection are eligible provided liver function meets eligibility criteria and are receiving management of the disease per local institutional practice (note: antiviral treatment for HCV is allowed with Sponsor approval). Subjects with history of COVID-19 must have recovered from the disease at least 30 days prior to randomization.

iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

v. Serious non-healing wound/ulcer/bone fracture.

vi. Malabsorption syndrome.

vii. Symptoms of thyroid dysfunction with thyroid function test corroboration (*Note: asymptomatic subjects with an isolated abnormal free thyroxine [FT4] are eligible*)

viii. Moderate to severe hepatic impairment (Child-Pugh B or C [Appendix J]).

ix. Requirement for hemodialysis or peritoneal dialysis.

x. History of solid organ transplant including liver transplant, or allogeneic stem cell transplant.

12. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Minor surgeries within 10 days before randomization. Subjects must have complete wound healing from major surgery or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

13. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 14 days before randomization.

    Note: If a single ECG shows a QTcF with an absolute value > 480 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

14. History of psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent

15. Pregnant or breastfeeding females.

16. Inability to swallow tablets.

17. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe hypersensitivity to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.

18. Any other active malignancy at time of randomization or diagnosis of another malignancy within 2 years before randomization that requires active treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy.

ESTIMATED LENGTH OF SUBJECT PARTICIPATION

It is estimated that subjects will receive study treatment for an average of approximately 6 months. Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect survival data.

ESTIMATED STUDY DATES

It is estimated that approximately 25 months will be required to randomize 740 subjects at approximately 250 global sites for the global enrollment phase of the study. The number of events required for the final analyses of the primary PFS (257 events among the first 372 randomized subjects within the cabozantinib + atezolizumab combination and sorafenib arms) and primary OS (368 events among the 555 randomized subjects within the cabozantinib + atezolizumab combination and sorafenib arms) is expected to be observed around approximately 18 months and around 38 months, respectively, after the first subject is randomized.

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. It is estimated that randomization of the subjects in mainland China during the global enrollment phase and Mainland China Extension Phase will require at least 21 months.

The true intervals required to meet the milestones above may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Subjects in the experimental arm will take oral study medication (40 mg of cabozantinib: 2 tablets containing 20 mg each of cabozantinib) once daily. Atezolizumab will be administered IV every 3 weeks at 1200 mg dose.

Dose reduction levels of cabozantinib will be allowed in the experimental arm (20 mg qd and 20 mg every other day [qod]). Dose reductions for atezolizumab will not be allowed and AEs will be managed by dose delays. Escalation of cabozantinib from 40 mg qd to 60 mg qd is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd.

Subjects in the control arm will take sorafenib orally (2 tablets containing 200 mg each of sorafenib) twice daily. Dose interruptions and reductions will be allowed as per local prescribing information.

Subjects in the single-agent cabozantinib arm will take 60 mg of cabozantinib qd (1 tablet of 60 mg of cabozantinib). Two dose reduction levels of cabozantinib will be allowed in this arm

(40 mg daily and 20 mg daily). Subjects may be allowed to re-escalate following a dose reduction according to the guidance provided in Section 6.6.1.

Subjects will continue study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator (see Section 5.8.6.3) or until unacceptable toxicity, the need for alternative anticancer treatment, or other reasons for treatment discontinuation. Continuation of one component of the combination study in the experimental arm (cabozantinib and atezolizumab) while discontinuing the other will be allowed as per protocol defined guidelines.

SAFETY ASSESSMENTS

Safety will be assessed on a schedule based on the date of the first dose (W1D1) and every 3 weeks thereafter. Routine safety follow-up visits will be performed 30 (+14) days (FU-1) and approximately 100 (± 14) days (FU-2) after the date of the decision to permanently discontinue study treatment. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix K.

Routine safety evaluations will include physical examination, vital signs, performance status, 12-lead ECG, hematology, serum chemistries, coagulation tests, urine tests (including UPCR), serum pregnancy tests (in females of childbearing potential), and thyroid function tests. Adverse event seriousness, severity grade, relationship to study treatment, and relationship to immune effects (ie, irAEs) will be assessed by the Investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v5.

An Independent Data Monitoring Committee (IDMC) will be established to monitor safety of the study on a regular basis. The IDMC will operate independently from the Sponsor and the clinical investigators.

EFFICACY ASSESSMENTS

Subjects will be monitored for radiographic response and progression per RECIST 1.1. For determining radiographic endpoints, radiographic assessments will be assessed by the BIRC and Investigator; radiographic assessment by the Investigator will be used for treatment decisions. Overall survival will be assessed at scheduled visits and every 12 weeks (± 14 days). Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data.

TUMOR ASSESSMENTS

Study Eligibility by Imaging-Based Diagnosis: Clinical diagnosis of HCC by multiphase imaging using CT or MRI in subjects with cirrhosis according to AASLD or EASL HCC guidelines is acceptable for study eligibility. Diagnostic imaging hallmarks of HCC include arterial phase enhancement, tumor size, washout, enhancing capsule, and threshold growth. If the subject does not have cirrhosis or these imaging criteria cannot be assessed or are not met, histological or cytological diagnosis of HCC is required for study participation. Ultrasound, angiography, fluorodeoxyglucose (FDG)-positron emission tomography (PET), or AFP cannot be used for clinical diagnosis of HCC. Accreditation for HCC diagnostic imaging, as described in the amended study imaging manual, is required before a site can enroll subjects diagnosed with HCC via imaging alone. Diagnostic scans may be used for screening if they meet the criteria described

in Section 5.8.6.2. For detailed guidance regarding diagnosis of HCC by imaging refer to the amended study imaging manual.

Chest / Abdomen / Pelvis (CAP): CT of CAP or CT chest and MRI abdomen/pelvis will be performed in all subjects at screening (prior to randomization). Tumor assessments after randomization should be performed every 6 weeks (± 7 days) though Week 49. After Week 49, these assessments will be performed every 12 weeks (± 7 days). CT/MRI of the CAP should include a noncontrast study of at least the liver followed by contrast with triphasic CT imaging of the liver or liver MRI with gadolinium enhanced imaging including triphasic liver.

Other Sites: All other known or suspected sites of disease, including in the brain or bone, are to be imaged by CT/MRI at screening (prior to randomization). Any lesions identified, including bone lesions with a soft tissue component, are to be followed at subsequent tumor assessments as described for CAP above using the same modality as at screening. New suspected lesion sites identified after randomization, including suspected sites of bone or brain lesions, should be assessed by CT/MRI. MRI is the preferred method for brain lesion assessment. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 8 weeks before randomization. Subjects without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.)

Tumor assessments should continue on the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued until a protocol-defined criterion for ending radiographic assessments is met (see Section 5.8.6.2). Treatment may continue after radiographic progression per RECIST 1.1 as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks (see Section 5.8.6.3). The same imaging modalities used at screening are to be used for subsequent tumor assessments after randomization.

Radiographic response and disease progression will be determined using RECIST 1.1. Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

Radiographic tumor assessments are to continue until the later of Investigator-determined radiographic progression per RECIST 1.1 or study treatment is permanently discontinued.

For the purpose of determining radiographic study endpoints, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments will be sent to the BIRC, which also will review prior radiation history data and prior local therapy information for the purpose of selection of target lesions.

TUMOR MARKER ASSESSMENTS

Tumor marker samples (AFP) will be collected at screening, predose on W1D1, and after first dose of study treatment as described in the schedule of assessments (Appendix A). The tumor marker assessments will not be used to determine PD in this study. The samples will be analyzed by a central laboratory.

PHARMACOKINETIC ASSESSMENTS

Blood samples will be obtained from all subjects in the experimental arm and the single-agent cabozantinib arms for cabozantinib PK. Samples will be collected for plasma cabozantinib concentration measurement predose on Week 1 Day 1 (W1D1), W4D1, W7D1, W10D1, and W13D1. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib in this population.

Blood samples will be obtained from all subjects in the experimental arm for atezolizumab PK. Samples will be collected for serum atezolizumab concentration measurement predose on W1D1, W4D1, W7D1, W10D1, W13D1 and FU visits. The results may be used to confirm exposure to atezolizumab.

Collection of PK samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

IMMUNOGENICITY ASSESSMENTS

Blood samples will be obtained from all subjects in the experimental arm (cabozantinib + atezolizumab) for immunogenicity assessment predose on W1D1, W13D1, W25D1, and at the Post-Treatment Follow-up visits (ie, FU-1 and FU-2). Collection of immunogenicity samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

BIOMARKER ASSESSMENTS

Peripheral blood samples will be obtained as specified in the Appendix A. Archival tumor tissue (most recently obtained) will be provided, if available. If archival tissue and histological/cytological confirmation of disease are not available, a tumor biopsy may be collected during screening with subject consent. An optional tumor biopsy may be collected approximately 6 weeks after the first dose of study treatment; other time points may be acceptable provided the tumor sample is collected prior to progressive disease. Exploratory analyses may include, but may not be limited to, the following:

- PD-L1 and MET and other relevant biomarkers in tumor specimens for association with clinical outcomes
- Immune cell infiltration and mutational load assessment in tumor specimens for association with clinical outcome
- Circulating immune cells in peripheral blood
- Blood biomarkers (ie, cytokines/chemokines, VEGF)
- Cell and/or plasma pharmacogenomics (eg, circulating tumor DNA [ctDNA])

Some biomarker samples may only be collected at selected sites (see the study laboratory manual for details). Collection of biomarker samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life assessments will be performed using the EuroQol Health questionnaire instrument EQ-5D-5L. Subjects will be requested to complete the assessment at

baseline (within 14 days prior to randomization) and every 6 weeks thereafter. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or the study meets its primary endpoints. Consequently these assessments may be required in the Post Treatment Period for some subjects. Subjects should complete the questionnaire on the day of the visit prior to seeing study site personnel. HRQOL assessments will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization parameters will be collected from randomization through the 100-Day Post-Treatment Follow-up Visit (FU-2). These include hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions. These data will not be collected in the Maintenance Phase.

STATISTICAL METHODS

The primary efficacy analyses in this study are the comparisons between the combination treatment and control arms for OS and PFS. These analyses will be performed for subjects enrolled in the global enrollment phase which will not include subjects enrolled in the Mainland China Extension Phase. Treatment with cabozantinib in combination with atezolizumab will be inferred to be superior to treatment with sorafenib if the null hypothesis of no difference between arms is rejected in favor of the experimental arm for either OS or PFS. Inflation of Type 1 error associated with multiple primary endpoints and the secondary efficacy endpoint of PFS between single-agent cabozantinib and sorafenib will be controlled by a closed testing procedure that employs a modified Bonferroni procedure, a gatekeeping technique, and the fallback method (see Section 9.5). The study-wise 2-sided alpha of 5% will be nominally divided between primary endpoints PFS (1%) and OS (4%), with the secondary PFS endpoint tested at the 1% level only if the primary PFS test is successful. If the null hypotheses are rejected for both the primary and secondary PFS endpoints, the 1% alpha for PFS will be reallocated to OS, allowing it to be tested at the 5% level.

Duration of OS is defined as time from randomization to death due to any cause. Duration of PFS is defined as time from randomization to the earlier of either PD per RECIST 1.1 as determined by the BIRC or death from any cause.

The primary analyses of OS and PFS will be event-driven and will be conducted independently after at least the number of events required for each analysis has been observed.

PFS and OS will be summarized descriptively using the Kaplan-Meier method. Inferential comparisons between treatment arms will use the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. Stratification will be based on the stratification factors used for the randomization as recorded in the Interactive Response Technology (IRT) system.

The study is designed to provide adequate power for analyses of both primary endpoints of PFS and OS comparing the experimental arm with the control arm, and for the analysis of the secondary endpoint of PFS comparing the single-agent cabozantinib arm with the control arm. For the primary endpoints, a larger sample size is needed to provide reasonable power for OS

than is required to evaluate PFS. As a result, if PFS were to be evaluated in the entire study sample required for OS, the PFS events may be biased toward shorter progression times. Thus, to allow longer, more robust PFS follow up among a smaller number of subjects this study employs a “trial within a trial design” (Hessel et al 2016).

The total sample size was planned to be 740 subjects randomized in a 2:1:1 fashion: 370 to the experimental combination arm (cabozantinib + atezolizumab), 185 to the control arm (sorafenib), and 185 to the single-agent cabozantinib arm. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects.

For primary PFS, a total of 257 events in the first 372 subjects randomized in a 2:1 ratio in the experimental and control arms (n=248 and 124, respectively; defined as the PFS Intent-to-Treat [PITT] population) provide the study with 90% power for a 2-sided log-rank test with a 1% level of significance to detect a hypothesized true HR of 0.6. Assuming an exponential distribution for PFS, this corresponds with a 67% increase in median PFS from 3.6 months to 6.0 months. The minimum observed effect that would result in statistical significance for PFS is an HR of 0.71, a 41% improvement in median from 3.6 to 5.1 months. Interim analysis of the primary PFS endpoint is not planned.

For OS, a total of 368 deaths among all 555 subjects randomized in a 2:1 ratio in the experimental (n=370) and control arms (n=185) are required to provide 90% power to detect an HR of 0.69 using the log-rank test and a 2-sided significance level of 4%. Assuming an exponential distribution for OS, this corresponds to a 45% increase in median survival from 12.3 months to 17.8 months. The minimum observed effect that would result in statistical significance for the primary analysis of OS is an HR of 0.7942, a 26% improvement in median from 12.3 to 15.5 months.

Two interim analyses of OS are planned and will include all subjects in the ITT population available at the time of each analysis. These are planned at the 33% and 66% information fractions. The first interim analysis (IA1) will coincide with the primary analysis of PFS and will be performed only if the null hypothesis for primary PFS is rejected and is expected to occur at approximately the 33% information fraction. Should the timing of IA1 trend towards an information fraction much higher than expected (eg, due to faster-than-expected deaths or slower-than-expected PFS events), the plan for the interim analyses of OS may be modified (see Section 9.8). Inflation of Type 1 error associated with these interim analyses will be controlled using Lan-DeMets O’Brien-Fleming (LD-OF) alpha-spending functions based upon a 4% total alpha allocation for OS.

The secondary analysis of PFS for the single-agent cabozantinib arm vs the control (sorafenib arm) will be performed for subjects enrolled in the global enrollment phase which will not include subjects enrolled in the Mainland China Extension Phase. For this analysis, a total of 283 events among all 370 subjects (185 per arm) in the single-agent cabozantinib and control arms provides the study with 85% power for a 2-sided log-rank test with a 1% level of significance to detect a hypothesized true HR of 0.65. Assuming an exponential distribution for PFS, this

corresponds with a 53% increase in median PFS from 3.6 months to 5.5 months. The minimum observed effect that would result in statistical significance for PFS is an HR of 0.735, a 36% improvement in median from 3.6 to 4.9 months.

An interim analysis of secondary PFS is planned contemporaneously with the primary PFS analysis and will include all subjects in single-agent cabozantinib and control arms of the ITT population available at the time of the analysis. This is anticipated to be at 67% information fraction (to be performed only if the null hypothesis for PFS is rejected). Inflation of Type 1 error associated with these interim analyses will be controlled using Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending functions based upon a 1% total alpha allocation for secondary PFS.

With a constant accrual rate of 30 subjects per month, it is anticipated that it will take approximately 18.4 months to observe the required primary PFS events (16.5 months of subject accrual) and approximately 38 months to observe the required deaths for OS (25 months of subject accrual) to evaluate the primary endpoints in the combination and control arms. Assuming the same accrual rate, it is anticipated that it will take approximately 25 months to observe the required secondary PFS events (25 months of subject accrual) to evaluate the secondary endpoint in the single-agent cabozantinib and control arms. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct.

The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined. The Mainland China Extension Phase will not be expanded beyond 148 subjects.

China Subpopulation: The primary scope of the China subpopulation analysis is to allow evaluation of consistency in efficacy and safety with the global study population per NMPA guidance. Since the China subpopulation is not powered to demonstrate statistical significance in terms of efficacy, no formal hypothesis testing will be performed. All data summaries for the China subpopulation will be descriptive. The safety and efficacy data in the China subpopulation will be analyzed separately for the same endpoints using the same analysis methods as for the global population. The analyses for this subpopulation will be performed when the data are of sufficient maturity to allow evaluation of consistency in efficacy and safety.

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AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AESI	adverse event of special interest
ACTH	adrenocorticotropic hormone
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-vs-time curve
BCAAs	branched-chain amino acids
BCLC	Barcelona Clinic Liver Criteria
bid	twice daily
BIRC	Blinded Independent Radiology Committee
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CAP	chest/abdomen/pelvis
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSC	Clinical Steering Committee
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	cytochrome P450
DICOM	Digital Imaging and Communications in Medicine
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis

EASL	European Association for the Study of the Liver
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA SmPC	European Medicines Agency Summary of Product Characteristics
ESC	Executive Safety Committee
ES-SCLC	extensive-stage small cell lung cancer
FACS	fluorescence-activated cell sorting
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone
FT4	free thyroxine
FU-1	first Post-Treatment Follow-up visit (30 [+14] days after decision to discontinue study treatment)
FU-2	second Post-Treatment Follow-up visit (100 [± 14] days after decision to discontinue study treatment)
GCP	Good Clinical Practice
GGT	γ-glutamyltranspeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HGF	hepatocyte growth factor
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQOL	health-related quality of life
HIV	human immunodeficiency virus
IA1	first interim analysis
ICF	informed consent form
ICH	International Conference on Harmonisation
ICI	immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IHC	immunohistochemistry
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board

IRF	independent radiology facility
IRR	infusion-related reaction
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	intravenous or intravenously
LD-OF	Lan-DeMets O'Brien-Fleming
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LMWH	low molecular weight heparins
LOLA	L-ornithine L-aspartate
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MTC	medullary thyroid cancer
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NPACT	nonprotocol anticancer therapy
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor 1
PD-L1	programmed death ligand 1
PEI	percutaneous ethanol injection
PFS	progression-free survival
PITT	PFS Intent-to-Treat
PK	pharmacokinetic or pharmacokinetics
PPE	palmar-plantar erythrodysesthesia
PPI	proton pump inhibitor
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
qnw	once every n weeks
qod	every other day

QTcF	Corrected QT interval calculated by the Fridericia formula
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RFA	radiofrequency ablation
RPLS	reversible posterior leukoencephalopathy syndrome
RSI	reference safety information
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SNP	single nucleotide polymorphism
TACE	transarterial chemoembolization
TARE	transarterial radioembolization
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TNBC	triple negative breast cancer
T_{reg}	regulatory T-cell
TSH	thyroid-stimulating hormone
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
US PI	US prescribing information
VAS	visual analog scale
VEGFR	vascular endothelial growth factor receptor
W#D#	Week # Day #
WBC	white blood cell

1. BACKGROUND

1.1. Hepatocellular Carcinoma

Liver cancer is the second most frequent cause of cancer deaths worldwide (Ferlay et al 2015). Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 90% of cases. In 2015, 854,000 new liver cancer cases were reported worldwide and 810,000 deaths occurred (Global Burden of Disease Liver Cancer 2017; EASL 2018). The estimated incidence and mortality rates of liver cancer in the USA in 2016 were approximately 42,000 and 30,000 cases, respectively (American Cancer Society 2018); incidence and mortality in the EU in 2012 were 52,000 and 48,000 cases, respectively (Ferlay et al 2013).

Surgical resection and transplantation are potential curative treatment modalities for HCC. Ablative therapies (eg, radiofrequency ablation [RFA], microwave ablation [MWA], and percutaneous ethanol injection [PEI]) are being used for early stage unresectable HCC. Transarterial chemoembolization (TACE) is used generally for intermediate stage disease. The current standard of care for the systemic treatment of advanced unresectable HCC is sorafenib, which is a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases. In a randomized placebo-controlled Phase 3 study (SHARP), sorafenib improved the primary endpoint of overall survival (OS) in subjects with Child-Pugh A advanced HCC who had not received prior systemic therapy (Llovet et al 2008). Median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.55, 0.87; p-value < 0.001). A similar HR was observed (with a shorter duration of OS than in the SHARP trial) in a corresponding placebo-controlled Phase 3 trial conducted in an Asian-Pacific population in which infection with hepatitis B virus (HBV) was the main cause of HCC: median OS was 6.5 months vs 4.2 months (HR 0.68; 95% CI: 0.50, 0.93; p-value = 0.014) (Cheng et al 2009). The VEGFR-targeting tyrosine kinase inhibitor (TKI) lenvatinib was shown to be non-inferior to sorafenib in subjects with advanced HCC who had not received prior systemic therapy (Kudo et al 2018) leading to US and EU approval in this population. In that study, median OS for lenvatinib was 13.6 months compared with 12.3 months for sorafenib (HR 0.92; 95% CI 0.79, 1.06).

Recently, immune checkpoint inhibitors (ICIs) that modulate the regulatory effects of programmed death receptor 1 (PD-1) with programmed death ligand 1 (PD-L1) have demonstrated activity in the treatment of HCC. The monoclonal antibody PD-1 inhibitor nivolumab was granted accelerated approval for the treatment of patients with HCC following prior sorafenib, regardless of PD-L1 status based on an objective response rate (ORR)

determined by blinded central review of 18.2% (n=154); 3.2% of subject achieved a complete response (CR). Another anti-PD-1 antibody, pembrolizumab, demonstrated encouraging ORR of 17% in sorafenib-pretreated HCC subjects in a single-arm Phase 2 study (Zhu et al [Lancet Oncol] 2018) and was also granted accelerated approval in the US for the treatment of patients with HCC previously treated with sorafenib.

1.2. Cabozantinib

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, AXL, and RET.

The RTK MET and its cognate ligand hepatocyte growth factor (HGF) play an important role in tumor pathobiology, including tumor growth, survival, neo-angiogenesis, invasion, and dissemination (Gherardi et al 2012). MET pathway activation and dysregulation have been implicated in multiple cancers, including HCC. Although its prevalence is not well characterized and may be influenced by source of tissue or methodology, MET has been found to be overexpressed in HCC compared with non-tumor liver tissue, with higher MET expression linked to poorer prognosis (Kaposi-Novak et al 2006, Kiss et al 1997, Ueki et al 1997). Moreover, small-molecule inhibitors of MET have been shown to exhibit efficacy in preclinical models of HCC (You et al 2011, Huynh et al 2012) and in early-phase clinical studies (Santoro et al 2013). The VEGFRs and ligands are central mediators of tumor neo-angiogenesis and lymphangiogenesis (Carmeliet et al 2011). High tumor microvessel density appears predictive of poor disease-free survival after HCC resection, and tumor vascular invasion is a well-established negative prognostic factor (Tanaka et al 1989, Greten et al 2009). Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway (Rimassa et al 2016, Rimassa et al 2018). Consistent with this, combined inhibition of VEGFR and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in tumor models (Aftab and McDonald 2011, Sennino et al [Cancer Discov] 2012, Sennino and McDonald [Nat Rev Cancer] 2012, You et al 2011).

In addition, other targets of cabozantinib are implicated in promoting tumor immune suppression including TYRO3, MER, and AXL (TAM family kinases). Preclinical studies (Kwilas et al 2014, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment that might present an opportunity for synergistic effects from combined treatment with ICIs.

Cabozantinib capsules (140 mg) are approved in the US 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, EMA SmPC). Cabozantinib tablets (60 mg) are approved in the US, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx™ US prescribing information [US PI], European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Based on the results from the studies described below, cabozantinib tablets (60 mg) have also been approved in the US and EU for the treatment of hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib (Cabometyx US PI and EMA SmPC).

The clinical activity and safety of cabozantinib (60 mg, tablets) in HCC has been demonstrated in a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects with advanced HCC who had received prior therapy with sorafenib (subjects were required to have progressed during or following prior systemic therapy and up to 2 prior lines of systemic therapy were allowed; Abou-Alfa et al 2018). A total of 773 subjects were enrolled. The primary endpoint of the study was OS. Up to three analyses of OS were planned: two interim analyses and a final analysis to occur when 311, 466 and 621 deaths (50%, 75% and 100%, respectively, of the total required number of events) had been observed. At the second pre-planned interim analysis, the prespecified event-driven primary efficacy endpoint analysis of the 707 subjects enrolled at the data cutoff (470 cabozantinib, 237 placebo), demonstrated a statistically significant improvement in OS for subjects in the cabozantinib arm compared with placebo (Intent-to-Treat [ITT] population): the HR, adjusted for stratification factors, was 0.76 (95% CI 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value to reject the null hypothesis of equal OS = 0.021). The Kaplan-Meier estimates for median duration of OS were 10.2 months in the cabozantinib arm vs 8.0 months in the placebo arm, an estimated 2.2-month difference in the medians. The landmark estimate of the proportion of subjects event-free at 12 months was 46% in the cabozantinib arm compared with 34% in the placebo arm. The secondary endpoint analysis of PFS as determined by the investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) yielded a median duration of PFS of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors, was 0.44 (95% CI 0.36, 0.52, stratified log-rank p-value < 0.0001). Investigator-determined ORR per RECIST 1.1 was 4% and 0.4% for subjects in the cabozantinib and placebo arms, respectively (unstratified Fisher exact test p-value = 0.0059); all were partial responses (PRs). In addition, there was a high rate of stable disease (SD) in the cabozantinib arm relative to placebo (60% vs 33%). Conversely, more subjects in the placebo arm had progressive disease (PD) as best overall

response (21% cabozantinib vs 55% placebo). In the cabozantinib arm of this HCC study, 99% of subjects experienced an adverse event (AE) regardless of causality, and 92% of subjects in the placebo arm had an AE. Adverse events reported for ≥ 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), fatigue, nausea, hypertension, vomiting, aspartate aminotransferase (AST) increased, and asthenia. Grade 3 or 4 AEs regardless of causality were reported for 68% of subjects in the cabozantinib arm and 36% in the placebo arm. Grade 3 or 4 AEs reported for ≥ 5% of subjects in the cabozantinib arm by decreasing frequency were PPE, hypertension, AST increased, fatigue, diarrhea, asthenia, and decreased appetite. The higher incidence of Grade 3 or 4 AEs in the cabozantinib arm compared with the placebo arm was mainly due to the higher incidences of PPE (cabozantinib 17%, placebo 0%) and hypertension (16%, 1.7%) of those grades. The results of this study were the basis for regulatory applications to the US FDA and EMA for treatment of patients with advanced HCC who have received prior therapy.

Earlier clinical evaluation of cabozantinib in HCC was conducted in a Phase 2 study that included both previously-treated and treatment-naïve subjects with advanced HCC (n=41; Kelley et al 2017). Progression-free survival from first dose throughout the study was estimated for all HCC subjects using a piecewise method; median PFS was 5.2 months. Tumor regression appeared independent of prior sorafenib exposure.

1.3. Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody which potently and selectively inhibits binding of PD-L1 on tumor cells and tumor infiltrating immune cells in the tumor microenvironment (McDermott et al 2016). Through this interaction, atezolizumab interrupts the negative regulatory effects of PD-L1 on T-cell proliferation and function that result from PD-L1 binding to PD-1 and B7.1 (CD80) expressed on T lymphocytes and other immune cells. The result is an increase in the susceptibility of tumor cells to T-cell-mediated immune response, an effect that has been demonstrated in clinical activity across several tumor types.

Atezolizumab injection, for intravenous (IV) use (1200 mg q3w), has been approved in the United States, the European Union, and other regions for the treatment of patients with advanced urothelial carcinoma (UC) after prior platinum containing chemotherapy or in a subset patients who are considered cisplatin-ineligible (different patient populations are indicated depending on region; Rosenberg et al 2016, Balar et al 2017). Atezolizumab is also approved for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy (Fehrenbacher et al 2016; Tecentriq™ US PI and EMA SmPC). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel protein-

bound for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). Regulatory approvals of atezolizumab are either based on prolongation of OS or PFS, increased response rate, or durable responses. Treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs).

In a Phase 1b study of atezolizumab (1200 mg q3w) in combination with the anti-VEGF targeting antibody bevacizumab by the data cutoff of 26 July 2018, 103 subjects with advanced HCC naïve to systemic therapy had been enrolled (NCT02715531; Pishvaian et al 2018) and were evaluable for safety; 73 of these subjects were evaluable for efficacy with a minimum follow-up period of 16 weeks. Among the efficacy-evaluable subjects, the median survival follow-up was 7.2 months. The ORR by independent radiology facility (IRF) was 27% (with 4 CRs) per RECIST 1.1 and was 34% (with 8 CRs) per mRECIST; ORR by Investigator per RECIST 1.1 was 32% with 1 CR. Confirmed responses were reported across the patient population regardless of HCC etiology, geographic region, baseline alpha-fetoprotein (AFP) levels, or extrahepatic spread of tumor. The investigator-assessed median PFS was 14.9 months (range: 0.5 to 23.9+ months) with a 6-month PFS rate of 65%; the IRF-assessed median PFS per RECIST 1.1 was 7.5 months (range: 0.4 to 23.9+ months). The median estimates for duration of response (DOR) and OS were not yet reached at the data cutoff. In the safety population (n=103), the most common (≥ 20% incidence) AEs were decreased appetite (28%), fatigue (20%), rash (20%), and pyrexia (20%). Treatment-related Grade 3 or 4 AEs were reported in 28 subjects (27%), most commonly hypertension (10 subjects [10%]). Five (5) Grade 5 AEs were observed, 2 of which were assessed as treatment related (one sepsis, one pneumonitis). Adverse events of special interest (AESIs) of any grade for atezolizumab were reported for 54% of subjects, and AESIs of any grade for bevacizumab were reported for 47% of subjects. Immune-related AESIs for atezolizumab of ≥ Grade 3 requiring corticosteroid treatment included pneumonitis (2 subjects), autoimmune encephalitis, drug-induced liver injury (DILI), colitis, AST increased, γ-glutamyltranspeptidase (GGT) increased, diabetes mellitus, and pancreatitis (1 subject each). A total of 19 subjects (18%) experienced treatment-related SAEs. The combination was considered well tolerated with no new safety signals beyond the established safety profiles of the individual agents. The high response rate observed suggested that the combination of atezolizumab with bevacizumab has synergistic activity in advanced HCC. Following these encouraging data, a Phase 3 study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic HCC has been initiated (NCT03434379).

These results improved upon the preliminary single-agent data with atezolizumab in subjects with treatment-naïve advanced HCC, in which few objective responses were observed (data provided by Roche):

- A Phase 1a study evaluating the safety, PK, and preliminary evidence of biologic activity of atezolizumab administered as a single agent included 15 subjects with advanced HCC; 5 subjects had not received prior systemic therapy (NCT01375842). For the 15 subjects with HCC, the median duration of treatment was 2 months (range: 0.7-6.3 months) at the time of data cutoff. There were no confirmed objective responses observed in the HCC subjects. The most commonly reported AEs (≥ 20%) in the HCC subjects (n=15) were fatigue and AST increased (40.0% each), diarrhea and nausea (33.3% each), ALT increased, thrombocytopenia, and decreased appetite (26.7% each), and pyrexia, anaemia, hypomagnesaemia, headache, and pruritus (20.0% each). Treatment-related ≥ Grade 3 AEs were AST increased (20.0%), ALT increased, blood ALP increased, blood bilirubin increased, and hepatocellular injury (6.7% each). Treatment-related SAEs occurred in 3 subjects and all were single occurrences (hepatocellular injury, device-related infection, and blood bilirubin increased).

- A second Phase 1 study evaluated the PK, safety, and preliminary anti-tumor activity of atezolizumab monotherapy in Chinese subjects with solid tumors (NCT02825940). Twenty-one subjects with HCC were enrolled; 7 subjects had not received prior systemic therapy. Of the 7 previously-untreated HCC subjects, 2 subjects had a confirmed objective response. The two confirmed responses were still ongoing at the time of the clinical cutoff date (duration of responses: 6.90+ and 5.55+ months; + denotes a censored observation). Median PFS was 1.5 months (95% CI: 1.4, not estimable) and median OS was 14.6 months (95% CI: 4.9, 14.6) for the previously untreated HCC subjects. The most commonly reported AEs (≥ 20%) in the HCC subjects were AST increased and blood bilirubin increased (47.6% each), ALT increased (42.9%), pyrexia and decreased appetite (28.6% each), blood ALP increased and fatigue (23.8% each). Treatment-related ≥ Grade 3 AEs were blood bilirubin increased, hypokalemia and hyponatremia, lymphocyte count increased (2 subjects), pyrexia, diplopia, anemia, febrile infection, and hypoglycemia. Treatment-related SAEs occurred in 5 subjects and included one subject each with Grade 3 hepatic function abnormal, Grade 3 ALT increased, Grade 2 AST increased, Grade 4 lipase increased, and one subject with Grade 4 hepatic failure and Grade 2 ascites.

Similarly, the response rate of single-agent bevacizumab had been previously reported as 13% (6 of 46 subjects; Siegel et al 2008), suggesting the high response rate observed with the

combination of atezolizumab and bevacizumab of the combination of atezolizumab and bevacizumab was not solely a result of either agent alone and resulted from synergistic activity between the two agents in advanced HCC.

1.4. Combination of Cabozantinib and Atezolizumab

Currently, atezolizumab is being evaluated in combination with cabozantinib (40 mg and 60 mg once daily orally) with atezolizumab (1200 mg intravenously [IV] q3w) in multiple tumor cohorts in multi-tumor cohort Phase 1b trial XL184-021 (NCT03170960). In the dose escalation stage of the study, there were no dose-limiting toxicities (DLTs) or SAEs at either dose level of cabozantinib evaluated. Through 21 August 2018, all the subjects in the dose escalation stage (n=12) were still receiving study treatment, with the median follow-up of 33.4 weeks of treatment (range: 26-50 weeks). The majority of AEs were of Grade 1 or 2 including irAEs. Grade 3 AEs included five events of hypertension, two events each of diarrhea and hypophosphatemia, and one event each of pulmonary embolism, hyperglycemia, GGT increased, AST increased, ALT increased, lymphocyte count decreased, lipase increased, muscular weakness, nephritis, and myositis (verbatim term). No Grade 4 or 5 AEs were reported. Among 10 evaluable subjects with clear cell RCC enrolled in the dose escalation stage, the investigator-assessed confirmed ORR was 70% with 1 CR and 6 PRs. Although both dose levels of 60 mg and 40 mg cabozantinib were considered tolerable without DLTs, 40 mg cabozantinib once daily (qd) in combination with the standard dose level of 1200 mg atezolizumab was considered the preferred dose level from a benefit/risk evaluation perspective due to its favorable safety profile over a prolonged time on study treatment with minimal dose reductions and encouraging preliminary efficacy. Subsequent to the decision to further evaluate the 40 mg cabozantinib dose in combination with atezolizumab, the Expansion Stage of the XL184-021 was initiated. As of 05 February 2019, 157 additional subjects had been enrolled in the expansion cohorts evaluating cabozantinib (40 mg, qd) + atezolizumab (1200 mg IV q3w). At the time of the cutoff, no subjects had been enrolled in the HCC cohort, which was added in a recent protocol amendment.

Through 29 January 2019, safety data were evaluable for 141 expansion stage subjects. At that time, the subject with the greatest treatment duration in the expansion stage had been receiving study treatment for approximately 11 months. The most frequently reported AEs (≥ 20% incidence) of any grade regardless of causality were fatigue (30%), diarrhea (28%), decreased appetite (24%), AST increased (22%), ALT increased (21%), and dysgeusia (21%). Grade 4 AEs irrespective of causality were reported for 10 subjects and comprised: AST increased, GGT increased, neutropenia, thrombocytopenia, CK increased, sodium decreased, hyperlipasemia, intestinal perforation, renal failure chronic, sepsis. Grade 5 AEs were reported for 9 subjects and

comprised: dehydration, transitional cell carcinoma (2 subjects with UC), disease progression (3 subjects), general physical health deterioration, hepatic failure, and intestinal obstruction. The Grade 5 event of dehydration was assessed as related to study treatment and occurred in a 90 year-old male with castration-resistant prostate cancer; the subject had significant co-morbidities prior to enrollment, including protein energy malnutrition with cachexia, ascites and edema.

1.5. Rationale

1.5.1. Rationale for Evaluating Cabozantinib in Combination with Atezolizumab in Advanced HCC

Targeting the VEGF-signaling pathway with small molecule TKIs has improved the clinical outcome of patients with advanced HCC; however, the OS benefit has been modest with a median OS between 10.7 and 13.6 months (Llovet et al 2008; Kudo et al 2018). More recently immune checkpoint therapies that inhibit the interaction between PD-1 and PD-L1 have shown encouraging clinical activity in VEGFR-TKI pretreated and VEGFR-TKI naïve subjects with advanced HCC (El-Khoueiry et al 2017). HCC is thought to be a good candidate for immunotherapies since liver carcinogenesis is closely linked to impaired anticancer immunity. For example, chronic liver inflammation in subjects with chronic liver disease leads to upregulation of the immune checkpoint PD-1/PD-L1, activation of immune suppressive cells such as regulatory T-cells (Tregs), and secretion of immunosuppressive cytokines, promoting immunotolerance and emergence and progression of HCC (Jenne and Kubes 2013; Xu et al 2006; Kassel et al 2009; Matsuzaki et al 2007). Besides the encouraging clinical data of single-agent ICIs in HCC there is a strong rationale to combine PD-1/PD-L1 targeting agents with multi-tyrosine kinase inhibitors such as cabozantinib or other VEGF-targeting drugs due to their potential synergistic effects in creating an immunopermissive environment (Khan and Kerbel 2018). Recent data from an ongoing Phase 1b trial evaluating an ICI (pembrolizumab) in combination with a VEGFR-TKI (lenvatinib) has shown that this combination is tolerable with encouraging antitumor activity (Ikeda et al 2018) with a response rate of 27% (confirmed responses) based on assessment of 26 subjects and a median PFS of 9.69 months. Similarly, a combination of atezolizumab with the VEGF targeting agent bevacizumab has demonstrated very encouraging preliminary clinical activity in subjects with advanced HCC with a response rate of 27% and a median PFS of 7.5 months based on independent radiological assessment per RECIST 1.1 of 73 subjects (Pishvaian et al 2018). Moreover, the combination of cabozantinib with atezolizumab has shown very encouraging clinical activity and tolerability in subjects with advanced cancer in a Phase 1b multi-tumor cohort study (refer to Section 1.4). Based on all of the above, further evaluation of cabozantinib in combination atezolizumab is warranted and has

the potential to improve the clinical outcome of subjects with advanced HCC due to synergistic activities of the two agents.

1.5.2. Rationale for Study Design

This study is a randomized, controlled Phase 3 study of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. The multiple primary endpoints are PFS by Blinded Independent Radiology Committee (BIRC) and OS.

Historically, OS has been used as a primary endpoint in clinical trials for HCC, a disease that long had very few treatment options, even after the approval of sorafenib. In the past two years, several agents have been approved for post-sorafenib therapy (eg, nivolumab in the United States and regorafenib worldwide), and lenvatinib has demonstrated non-inferiority to sorafenib for previously untreated patients leading to US and EU approval in that population, providing another potential treatment option. Regorafenib improved overall survival after progression on sorafenib in subjects with prior sorafenib tolerance in the RESORCE trial (Bruix et al 2017), leading to approval in this population. Recently, ramucirumab has demonstrated improved OS and PFS versus placebo in patients with elevated (≥ 400 ng/mL) baseline AFP following sorafenib treatment as the first biomarker-selected treatment in HCC (Zhu et al [J Clin Oncol] 2018). Nivolumab was the first checkpoint inhibitor approved by FDA in advanced HCC based upon promising ORR in the non-randomized Checkmate-040 trial (El-Khoueiry et al 2017). In addition, FDA granted accelerated approval for pembrolizumab in sorafenib-pretreated advanced HCC based on promising ORR (17%) in the non-randomized KEYNOTE-224 study (Zhu et al [Lancet Oncol] 2018).

Given the multiple treatment options currently available and the changing treatment landscape in advanced HCC, subsequent anticancer therapy may confound the effect on OS in treatment-naïve subjects. Further, in the double-blinded, placebo-controlled Phase 3 study of cabozantinib in previously-treated HCC, a statistically significant improvement in both OS and PFS (per investigator assessment) for cabozantinib was demonstrated (refer to Section 1.2). Based on these data, cabozantinib (60 mg tablets) has been approved in the US and EU for treatment of patients with HCC who were previously treated with sorafenib. These approvals introduce the potential for off-study crossover for the subjects randomized to the sorafenib arm in the proposed study in the regions where cabozantinib is commercially available.

Also, a meta-analysis conducted using data from 10 studies with a total of 20 treatment arms and 6689 subjects suggests that either time to progression (TTP) or PFS could serve as a surrogate marker for OS in the clinical trials of advanced HCC (Lee et al 2016).

Therefore, PFS may provide an important indicator of clinical benefit in first line subjects and has been chosen as a multiple primary endpoint for this trial. For the purpose of evaluating radiographic study endpoints, a BIRC will be used to minimize bias in this open-label study. Given the importance of OS as an endpoint in HCC, OS will also be a multiple primary endpoint and will be analyzed whether or not the PFS analysis is positive. In order to avoid confounding the analysis of OS, crossover between treatment arms within the study will not be allowed until all endpoints of the study are available and shown to sufficiently support the safety and efficacy of the combination of cabozantinib + atezolizumab.

In recent years regulatory agencies have issued guidance for evaluating combination therapies requiring nonclinical and clinical evidence that supports the need for both components of the treatment regimen. In light of this guidance, direct discussions with regulatory agencies, and the limited amount of clinical data available for the administration of cabozantinib in the first-line HCC setting, a third treatment arm (approximately 185 subjects) will be enrolled in which subjects receive single-agent cabozantinib in order to determine its contribution to the overall safety and efficacy of the combination with atezolizumab in this patient population. Given the statistically significant improvement in OS and PFS demonstrated with single-agent cabozantinib in a previously treated HCC population and subsequent regulatory approval for cabozantinib to treat those patients, early observations of clinical activity in a previously untreated HCC population, and the demonstration of efficacy of other VEGFR-TKIs (eg, sorafenib, lenvatinib) in a previously untreated HCC population, exploration of cabozantinib (at the recommended single-agent dose of 60 mg) in a previously untreated HCC population is justified. A formal planned analysis of PFS for the single-agent cabozantinib arm vs the control arm (sorafenib) as a secondary endpoint will evaluate the relative efficacy of those two agents and will provide the basis for establishing the contribution of cabozantinib to combination therapy administered in the experimental arm.

In order to evaluate the full clinical benefits of the combination therapy of cabozantinib with atezolizumab, the current Phase 3 study includes analyses of health-related quality of life (HRQOL), healthcare resource utilization, pharmacokinetics (PK), and biomarkers.

It is planned to include up to 148 subjects from mainland China in this study to assess safety and efficacy in the China subpopulation. In the event enrollment in mainland China is incomplete by the time the global enrollment phase has been completed, a Mainland China Extension Phase will be implemented to complete enrollment and facilitate subpopulation analyses as needed. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).

1.5.3. Rationale for Study Treatment Dose Selection and Treatment Schedule

In accordance with the standard approved dose, atezolizumab 1200 mg will be administered as an IV infusion over 60 min (± 15 min) every 3 weeks (± 2 days) on Day 1 of each 21-day cycle (Tecentriq US PI, SmPC).

The approved tablet dose level for the single-agent treatment of advanced RCC is 60 mg and was also the dose used for the evaluation of cabozantinib as a single agent in the Phase 3 CELESTIAL study in previously treated HCC, which supported the recent approvals of that dose for the treatment of HCC following previous treatment with sorafenib in the US and EU. Dose reductions to 40 mg and 20 mg are utilized to manage AEs. In the Phase 3 CELESTIAL study in HCC, the average daily dose was 35.8 mg/day, taking into account dose modifications.

In the Dose-Escalation Stage of the Phase 1b study XL184-021 evaluating the combination of cabozantinib with atezolizumab, cabozantinib was administered orally daily at dose levels of 40 and 60 mg in escalation cohorts (NCT03170960). A total of 12 subjects with advanced RCC were enrolled, six subjects at each cabozantinib dose level (40 mg and 60 mg). After reviewing safety data at both dose levels, the Cohort Review Committee determined that cabozantinib 40 mg qd orally in combination with 1200 mg atezolizumab q3w IV would be the recommended dose for further evaluation in the Expansion Stage of the study in multiple tumor types; the Expansion Stage is currently ongoing. The 40-mg dose was also determined to be the recommended dose for cabozantinib in the clinical evaluation of the combination of cabozantinib with nivolumab, another antibody inhibitor of the PD-1/PD-L1 pathway (Apolo et al 2016).

A safety summary with a data cutoff date of 21 August 2018 of the XL184-021 Dose-Escalation Stage showed that all 12 enrolled subjects were still active. The median duration of follow-up at that time was 33.4 weeks (range: 26-50 weeks). The majority of all-causality AEs at both dose levels (cabozantinib 40 and 60 mg) were of Grade 1 and 2 in severity and there were no Grade 4 or 5 events. Grade 3 AEs at the cabozantinib 40 mg dose level included hypertension (n=3),

hypophosphatemia (n=1), pulmonary embolism (n=1), hyperglycemia (n=1), GGT increased (irAE, n=1), muscular weakness (n=1), and myositis (verbatim term, irAE, n=1). Grade 3 AEs at the cabozantinib 60 mg dose level included hypertension (n=2), diarrhea (n=2), AST increased (irAE, n=1), ALT increased (irAE, n=1), hypophosphatemia (n=1), lipase increased (irAE, n=1), lymphocyte count decreased (n=1), and nephritis (n=1). All AEs were manageable by dose modifications including dose reductions and dose delays as well as supportive care. Both assigned dose levels of cabozantinib (40 mg and 60 mg) were well tolerated over extended dosing periods with no DLTs during the Dose-Escalation Stage, and confirmed responses were observed. However, there was a higher rate of dose reductions (cabozantinib) and dose delays (atezolizumab) in subjects enrolled at the cabozantinib 60 mg dose level, suggesting that the longer term tolerability of the combination was improved at the cabozantinib 40 mg dose level. The overall safety profile of each study treatment component remained consistent with previous reports. A safety overview for the two dose level cohorts explored in the Dose-Escalation Stage is shown in Table 1.

Table 1: Summary of Safety Events in the Dose-Escalation Stage of Study XL184-021 through 21 August 2018

Event	Cabozantinib 40 mg + Atezolizumab 1200 mg (N=6)	Cabozantinib 60 mg + Atezolizumab 1200 mg (N=6)
DLT	0	0
SAE	0	0
Grade 3 AE	5 (83%)	6 (100%)
Grade 3 Immune-related AE (irAE)	1 (17%)	2 (33%)
AE leading to cabozantinib dose reduction	3 (50%)	6 (100%)
AE leading to atezolizumab dose delay	1 (17%)	4 (67%)

AE, adverse event; SAE, serious adverse event.

As of 11 February 2019, 11 of the 12 subjects continue on study treatment. The first subject enrolled in the Dose Escalation Stage discontinued in January 2019, after 15+ months on study treatment.

Subsequent to the decision to further evaluate the 40 mg cabozantinib dose in combination with atezolizumab, the expansion stage of the XL184-021 was initiated. As of 05 February 2019, 157 additional subjects had been enrolled in the expansion cohorts evaluating cabozantinib (40 mg, qd) + atezolizumab (1200 mg IV q3w); information on the 141 subjects evaluable for safety as of 29 January 2019 is provided in Section 1.4.

1.6. Overall Risk Benefit Assessment

Liver cancer is the second most frequent cause of cancer deaths worldwide (Ferlay et al 2015). Hepatocellular carcinoma is the most common form of primary liver cancer, accounting for approximately 90% of cases. In 2015, 854,000 new liver cancer cases were reported worldwide and 810,000 deaths occurred (Global Burden of Disease Liver Cancer 2017; EASL 2018). The estimated incidence and mortality rates of liver cancer in the USA in 2016 were approximately 42,000 and 30,000 cases, respectively (American Cancer Society 2018); incidence and mortality in the EU in 2012 were 52,000 and 48,000 cases, respectively (Ferlay et al 2013).

Cabozantinib is a potent inhibitor of multiple RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, AXL, and RET. Recently, a randomized placebo-controlled Phase 3 study (CELESTIAL) of cabozantinib (60 mg, tablets) in subjects with advanced HCC who had received prior therapy with sorafenib has been conducted. The study met its primary endpoint of improving survival of subjects treated with cabozantinib, and the safety and tolerability of cabozantinib in that population was established in the study (Abou-Alfa et al 2018). The results of this study (see Section 1.2) lead to the approval in the US FDA and EU for treatment of patients with advanced HCC who have received prior sorafenib. Early evaluation of cabozantinib in previously treated and untreated HCC subjects showed clinical activity regardless of prior therapy.

Recently, immunotherapies have expanded treatment options for subjects with advanced HCC. For example, nivolumab, a PD-1 targeting ICI received accelerated approval in the United States based on response rate and response duration for the treatment of subjects with advanced HCC who have been previously treated with sorafenib (Opdivo US PI; NCCN V3.2018). A Phase 3 trial evaluating nivolumab in treatment-naïve advanced HCC is ongoing (NCT02576509). Similarly, pembrolizumab, another PD-1 inhibitor, has received accelerated approval for the treatment of HCC patients who have received prior sorafenib, and is being further evaluated in combination with lenvatinib in a previously untreated population. In addition, based on very encouraging early clinical stage study results, atezolizumab is also being evaluated in a Phase 3 trial in combination with bevacizumab compared with sorafenib in subjects with untreated locally advanced or metastatic HCC (NCT03434379).

The combination dosing regimen of cabozantinib and atezolizumab for the current study is based on the dose finding results in the ongoing Phase 1b combination study (NCT03170960) and is expected to mitigate potential overlapping AEs and improve long-term tolerability of the regimen. The dose in the single-agent cabozantinib arm has demonstrated improved OS and PFS in RCC and previously treated HCC.

In this study subjects will be allowed to receive treatment as long as they continue to experience clinical benefit in the opinion of the investigator (see Section 5.8.6.3) or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5).

Study inclusion/exclusion criteria were designed to prevent subjects at a heightened safety risk from entering the study (Section 4.2 and Section 4.3). The protocol provides guidance to investigators for the management of important AEs that are associated with cabozantinib, atezolizumab, and sorafenib (Section 6.6.2). Frequent safety assessments including laboratory assessments allow identification and early intervention of potential AEs due to study treatment.

An Independent Data Monitoring Committee (IDMC) will monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in conducting studies in oncology. Additionally, the Sponsor's safety committee will monitor the safety of the study on a regular basis.

1.6.1. Summary of Benefits and Risks

Cabozantinib and atezolizumab have demonstrated clinical activity as single agents and in combination with other drugs in various tumor types including HCC. In addition, in the ongoing Phase 1b study the combination of cabozantinib with atezolizumab has been well tolerated and demonstrated encouraging clinical activity indicating possible synergistic effects of both agents in subjects with advanced cancer. The safety profile of each agent is well defined, and dose modification guidelines have been established and used in previous clinical studies to effectively manage side effects. The combination therapy of atezolizumab and cabozantinib provides a new treatment opportunity with a manageable safety profile for subjects with advanced HCC who normally have a 5-year survival of less than 10%. The clinical activity of the combination is expected to be superior to treatment with either agent alone.

1.7. Study Conduct

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines and also consistent with the most recent accepted version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel for whom sanctions have been invoked or there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment, etc).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is to evaluate the efficacy of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. A secondary objective is to evaluate the single-agent activity of cabozantinib compared with sorafenib in this patient population.

2.2. Endpoints

Primary Efficacy Endpoints:

- Duration of PFS per RECIST 1.1, by BIRC for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib)
- Duration of OS for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib)

Secondary Efficacy Endpoints:

- PFS per RECIST 1.1 by BIRC for the single-agent cabozantinib arm vs the control arm (sorafenib)

Additional Endpoints:

- ORR, TTP, and DOR per RECIST 1.1 by BIRC and Investigator
- Evaluation of radiographic response per modified RECIST (mRECIST)
- Safety through the evaluation of AEs, including irAEs and other AESIs
- Characterization of the PK of cabozantinib in subjects with previously untreated HCC
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Change in serum AFP from baseline
- Correlation of biomarker analyses with clinical outcomes
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)
- Healthcare resource utilization

3. STUDY DESIGN

3.1. Study Sites

This study will be conducted at approximately 250 global clinical sites.

3.2. Estimated Study Dates and Duration of Subject Participation

It is estimated that it will take approximately 25 months to randomize 740 subjects in the ITT population for the primary and secondary analyses at approximately 250 global sites. The number of events required for the final analysis of one of the endpoints of PFS (257 events among the first 372 subjects randomized to the cabozantinib + atezolizumab combination and sorafenib arms) is expected to be observed approximately 18 months after the first subject is randomized. The number of events required for the final analysis of OS (368 events among the 555 subjects randomized to the cabozantinib + atezolizumab combination and sorafenib arms) is expected to be observed approximately 38 months after the first subject is randomized.

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. It is estimated that randomization of the subjects in mainland China during the global enrollment phase and Mainland China Extension Phase will require at least 21 months.

The true intervals required to meet the milestones above may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct.

It is estimated that subjects will participate for an average of 6 months on study treatment. Some study assessments continue periodically after study treatment is discontinued, and subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data.

3.3. Overview of Study Design

This is a multicenter, randomized, open-label, controlled Phase 3 trial of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. PFS and OS are multiple primary efficacy endpoints. Additionally there will be a third arm to evaluate the single-agent safety and activity of cabozantinib. Approximately 740 eligible subjects with advanced HCC were planned to be randomized in a 2:1:1 ratio at approximately 250 sites in this trial to receive study treatment in

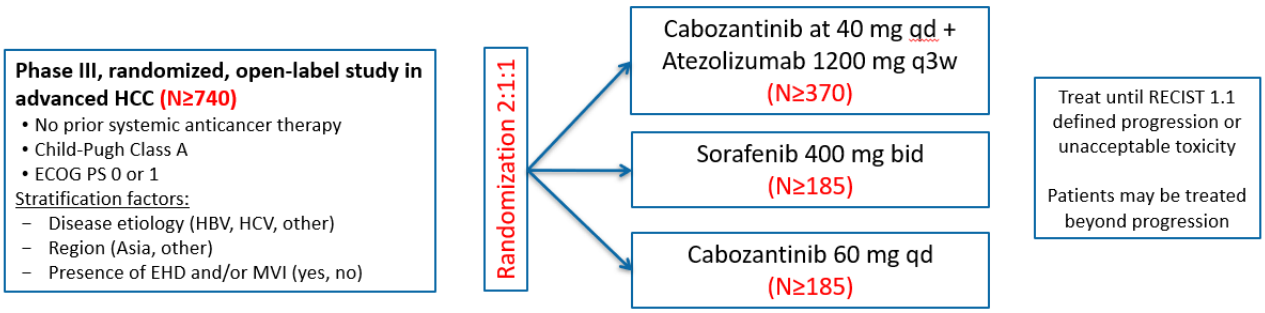
the global enrollment phase of the study as described in Section 3.3. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects.

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).

The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined. The Mainland China Extension Phase will not be expanded beyond 148 subjects.

Special accommodations during the global COVID-19 pandemic are described in Appendix M.

Figure 1: XL184-312 Study Schema



The trial consists of the following phases:

Pre-Treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Guidance for diagnosis of HCC in cirrhotic patients by imaging is provided in Section 5.8.6.1.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1:1 manner to receive study treatment as follows:

Experimental arm (at least 370 subjects):

Cabozantinib (40 mg oral, qd) +

Atezolizumab (1200 mg infusion, q3w)

Control arm (at least 185 subjects):

Sorafenib (400 mg, twice a day [bid])

Single-Agent Cabozantinib Arm (approximately 185 subjects):

Cabozantinib (60 mg qd)

Details about the investigational regimens are provided in Section 6.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator (see Section 5.8.6.3) or until there is unacceptable toxicity, the need for subsequent systemic anticancer treatment, or any other reasons for the treatment discontinuation listed in the protocol (Section 3.5). Subjects are allowed to discontinue one component of the experimental arm (cabozantinib and atezolizumab) but continue to receive the other. Crossover from the control or single-agent cabozantinib arms to experimental therapy will not be allowed unless study transitions to a Crossover Phase.

Crossover Phase: The study may transition to a Crossover Phase if the analysis of the primary endpoint of OS for the global ITT population (ie, not including subjects enrolled in the Mainland China Extension Phase) shows statistically significant and clinically meaningful evidence of improvement.

The Crossover Phase will only be implemented upon decision by the Sponsor and following any required discussion with regulatory authorities following review of the data. Crossover may be implemented independently and at different points in time for study sites and subjects in

mainland China compared to other sites and subjects in the global study. If the decision is made to enter the Crossover Phase, study sites will have 8 weeks to determine eligibility and begin administration of crossover treatment (cabozantinib + atezolizumab combination) to eligible subjects randomized to the control arm (sorafenib) or the single-agent cabozantinib arm; subsequently no further crossover will be allowed.

The study is expected to have completed enrollment in the global enrollment phase at the time of transitioning to the Crossover Phase for subjects who enrolled in that phase, but accrual of subjects in the Mainland China Extension Phase may still be ongoing at that point. In the Crossover Phase safety and efficacy assessments will continue as scheduled; PK, biomarker, HRQOL, and healthcare resource utilization assessments will be discontinued.

Post-Treatment Period: A first Post-Treatment Follow-up visit (FU-1) for safety evaluation (including subjects in the Maintenance Phase [below]) is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second Post-Treatment Follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix K.

Radiographic tumor assessments and HRQOL assessments are to continue, regardless of whether study treatment is given, reduced, held or discontinued until a protocol-defined criterion for ending radiographic assessments is met (see Section 5.8.6.3). Consequently these assessments may be required in the Post-Treatment Follow-up Period for some subjects.

In addition, subjects are to be contacted every 12 weeks (± 14 days) after FU-2 to assess survival status and document receipt of subsequent anticancer therapy. This follow-up will continue until the subject expires or the Sponsor decides to discontinue collection of these data; however, these assessments are not required in the Maintenance Phase (below). Every effort must be made to perform these evaluations unless consent is withdrawn.

Mainland China Extension Phase: After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. The Pre-Treatment, Treatment, and Post-Treatment Periods of the study will be conducted in the same manner in the Mainland China Extension Phase as for subjects who were enrolled in the global enrollment phase.

Study Completion: The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS (experimental vs control arm) in either of the two planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results) and any required supportive analyses for China are completed.

Maintenance Phase/Treatment After Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, subjects who continue study treatment may enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analyses required for regulatory purposes to have been completed. If a Crossover Phase has been implemented, the Maintenance Phase may not begin before the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last subject randomized to sorafenib or single-agent cabozantinib who crossed over to receive cabozantinib + atezolizumab. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects will continue to receive study treatment until they meet the protocol-required criteria for treatment discontinuation. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments. The nature and frequency of these assessments during the Maintenance phase are to be performed per institutional standard of care and guidance from the sponsor (see Appendix B). It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of SAEs; certain AEs (including irAEs and other AESIs [whether serious or not], and AEs leading to dose modifications or treatment discontinuation); and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

The study clinical database will be closed upon initiation of the Maintenance Phase. Important safety information (noted above) collected in the Maintenance Phase will be captured in the safety database. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

End of Trial: End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

3.4. Treatment Groups and Randomization

After obtaining informed consent, the site representative will use the designated web-based interactive response technology (IRT) system to register a subject. The IRT will assign a unique subject number. When a subject has been deemed eligible at the study site, the site representative will use the IRT to randomize and enroll the subject into the study.

Eligible subjects will be randomly assigned in a 2:1:1 ratio to the following treatment arms:

- Experimental arm: Cabozantinib (40 mg oral, qd) + atezolizumab (1200 mg infusion, q3w)
- Control arm: Sorafenib (400 mg, bid)
- Single-agent cabozantinib arm: Cabozantinib (60 mg oral, qd)

Details about treatment regimens are provided in Section 6.

Randomization will be stratified by the following factors established at screening:

- Disease etiology (HBV [with or without hepatitis C virus {HCV}], HCV [without HBV], or Other)
- Region (Asia, Other)
- Presence of extrahepatic disease and/or macrovascular invasion (Yes, No)

Randomization should occur as close as possible to the planned start of treatment (ie, within 3 days). Subjects are defined as enrolled in the study if randomized. Changes to stratification values entered in the IRT will not be performed after randomization. Randomization will not be voided except under very rare circumstances and with Sponsor approval. Subjects who sign consent, are assigned a subject identifier, and are screened (to any degree, including rescreening) but never randomized are deemed permanent screen failures.

If initiated, subjects recruited in the Mainland China Extension Phase will be randomized according to the same 2:1:1 scheme as subjects in the global enrollment phase.

3.5. Treatment Discontinuation and Withdrawals

Details for handling treatment discontinuation and study withdrawal are discussed in Sections 3.5.1 and 3.5.2, respectively.

If a subject requests to discontinue study treatment and/or withdraws study consent, the Investigator must establish the specific nature of the subject's request.

The subject's decisions (there may be more than one over time) must be recorded in source documents and transcribed to study case report forms (CRFs).

3.5.1. Treatment Discontinuation

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment and assessments or withdraw their consent to participate in the study at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in source documents and all study treatment will be stopped. The Investigator may also discontinue a subject from study treatment if in his or her clinical judgment it is in the best interest of the subject or if the subject cannot comply with the protocol. In addition, the investigator will also discontinue a subject from study treatment upon the Sponsor's request or if the Sponsor chooses to terminate the study.

Furthermore, any of the following conditions require withdrawal of the subject from study treatment:

- Unacceptable side effects the Investigator feels may be due to study treatment. Continuation of one component of the combination study treatment while discontinuing the other will be allowed. The Investigator is encouraged to consult with the Sponsor before discontinuing subjects from study treatment.
- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention.
- Necessity for treatment with nonprotocol systemic anticancer therapy.
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment related AEs unless approved by the Sponsor. (Note: temporary interruptions of study treatment for greater than 12 weeks due to the effects of COVID-19 and unrelated to AEs are described in Appendix M)
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use highly effective methods of contraception (Appendix H).
- Female subjects who become pregnant.
- Request by the Sponsor.
- Significant noncompliance with the protocol schedule in the opinion of the Investigator or the Sponsor.

To ensure timely Sponsor notification of study treatment discontinuations, site personnel are to promptly record treatment discontinuations in the study IRT. The reason for study treatment discontinuation must be recorded in source documents and case report forms (CRFs). If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter requesting contact with the clinic should be sent to the subject (or the subject's legal guardian).

For subjects who discontinue study treatment, every effort must be made to undertake protocol-specified follow-up procedures including end-of-treatment assessments, survival follow-up, and documentation of subsequent anticancer treatment(s) unless consent for noninterventional study treatments is also withdrawn. If a subject is discontinued from study treatment because of an AE (including AESI; Table 31) considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

Specific criteria for discontinuation of cabozantinib are provided in Section 6.6.2.1, for discontinuation of atezolizumab are provided in Section 6.6.2.2, and for sorafenib are provided in Section 6.6.2.3.

3.5.2. Study Withdrawal

Upon discontinuation of study treatment, at any time without prejudice, subjects may:

- Continue study interventions (eg, examination, blood and tissue sampling radiographic assessments, questionnaires) and non-interventional study assessments (eg, medical record review, survival contacts), or
- Withdraw their consent for study interventions but continue non-interventional study assessments, or
- Withdraw their consent for both study interventions and non-interventional study assessments.

Reasons for study withdrawal will be recorded in the source documents and CRFs. As applicable, no further study procedures or assessments will be performed or study data collected. For subjects who withdraw consent, determination of survival status from public records such as government vital statistics or obituaries will be performed as allowed by local regulations. Subjects who withdraw from the study will not be replaced.

3.5.3. Study Completion

The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS (experimental vs control arm) in either of the two planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results), all other planned formal inference tests have been performed (eg, for secondary efficacy endpoints), and any required supportive analyses for China are completed.

3.5.4. End of Trial

End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

4. STUDY POPULATION

4.1. Target Population

This study will enroll subjects with treatment-naïve advanced HCC. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that subjects fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

4.2. Inclusion Criteria

1. Histological or cytological diagnosis of HCC or clinical diagnosis of HCC in cirrhotic patients by multiphase imaging using CT or MRI per the American Association for the Study of Liver Diseases (AASLD) (Marrero et al 2018) or European Association for the Study of the Liver (EASL 2018) guidelines.

   Note: Sites must receive Sponsor accreditation for imaging-based diagnosis of HCC prior to implementing this methodology. In addition, subjects who do not meet the AASLD or EASL guidelines for imaging diagnosis of HCC or who do not have cirrhosis must have histological or cytological diagnosis of HCC.

2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE).

3. The subject is receiving antiviral therapy per local standard of care if the subject has active HBV infection (defined by HBsAg positive); the subject must have HBV DNA < 500 IU/mL.
4. Measurable disease per RECIST 1.1 as determined by the Investigator.

5. Barcelona Clinic Liver Cancer (BCLC) stage Category B or C (Appendix I).

6. Child-Pugh Score of A (Appendix J).

7. Recovery to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy as determined by the Investigator.

8. Age eighteen years or older on the day of consent.

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization:

    a. Absolute neutrophil count (ANC) ≥ 1500/µL (≥ 1.5×10^9/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.

    b. White blood cell (WBC) count ≥ 2000/µL (≥ 2.0×10^9/L).

    c. Platelets ≥ 60,000/µL (≥ 60×10^9/L) without transfusion within 2 weeks before screening laboratory sample collection.

    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 2 weeks before screening laboratory sample collection.

    e. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)

    f. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) ≤ 5 × upper limit of normal (ULN).

    g. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L).

    h. Serum albumin ≥ 2.8 g/dL (≥ 28 g/L).

    i. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 3).

    j. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h protein ≤ 1 g.

11. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessment except those procedures performed as standard of care within the screening window.

12. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix H) during the course of the study and for 5 months after the last dose of study treatment. A barrier method (eg, condom) is also required.

13. 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 is 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 hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

4.3. Exclusion Criteria

1. Known fibrolamellar carcinoma, sarcomatoid HCC or mixed hepatocellular cholangiocarcinoma.

2. Prior systemic anticancer therapy for advanced HCC including but not limited to chemotherapy, small molecule kinase inhibitors, and ICIs. Subjects who have received local intratumoral or arterial chemotherapy are eligible.

3. Documented hepatic encephalopathy (HE) within 6 months before randomization (see Section 6.6.2.4 for a case definition of HE).

4. Clinically meaningful ascites (ie, ascites requiring paracentesis or escalation in diuretics) within 6 months before randomization.

5. Subjects who have received any local anticancer therapy including surgery, PEI, RFA, MWA, transarterial chemoembolization (TACE), or transarterial radioembolization (TARE) within 28 days prior to randomization

6. Radiation therapy for bone metastasis within 2 weeks, any other external beam radiation therapy within 8 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 8 weeks prior to randomization. Subjects who are neurologically symptomatic or are receiving systemic corticosteroid treatment at the planned time of randomization are not eligible.

8. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:

    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)

9. Administration of a live, attenuated vaccine within 30 days prior to randomization.

10. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents.

11. The subject has uncontrolled, significant intercurrent or recent (within the last 3 months before randomization [unless otherwise specified below]) illness including, but not limited to, the following conditions:

    a. Cardiovascular and cardiac disorders:

        i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, 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 (eg, DVT, pulmonary embolism) within 6 months before randomization.

        iv. History of risk factors for torsades de pointes (eg, long QT syndrome).

    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

        i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra-abdominal abscess must be confirmed prior to randomization.

iii. Gastric or esophageal varices that are untreated or incompletely treated with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months before randomization are eligible.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major blood vessel, including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the intrahepatic vasculature, including portal vein, hepatic vein, and hepatic artery, are eligible.

f. Other clinically significant disorders such as:

i. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix D for a more comprehensive list of autoimmune diseases and immune deficiencies). Subjects with the following conditions are eligible for the study:

- A history of autoimmune-related hypothyroidism and on thyroid replacement hormone
- Controlled Type 1 diabetes mellitus and on an insulin regimen
- Asthma that requires intermittent use of bronchodilators
- Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true:

- Rash covers < 10% of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- 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

ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before randomization.
Note: Inhaled, intranasal, intra-articular, and topical corticosteroids and mineralocorticoids are permitted.

Transient use of systemic corticosteroids for allergic conditions such as contrast allergy is allowed.

iii. Active infection requiring systemic treatment, 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. Subjects with active hepatitis B virus infection controlled with antiviral therapy are eligible (see Inclusion Criterion 3). Subjects with active, uncontrolled hepatitis C virus infection are eligible provided liver function meets eligibility criteria and are receiving management of the disease per local institutional practice (note: antiviral treatment for HCV is allowed with Sponsor approval). Subjects with history of COVID-19 must have recovered from the disease at least 30 days prior to randomization.

iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

v. Serious non-healing wound/ulcer/bone fracture.

vi. Malabsorption syndrome.

vii. Symptoms of thyroid dysfunction with thyroid function test corroboration (*Note: asymptomatic subjects with an isolated abnormal free thyroxine [FT4] are eligible*).

viii. Moderate to severe hepatic impairment (Child-Pugh B or C [Appendix J]).

ix. Requirement for hemodialysis or peritoneal dialysis.

x. History of solid organ transplant including liver transplant, or allogeneic stem cell transplant.

12. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Minor surgeries within 10 days before randomization. Subjects must have complete wound healing from major surgery or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

13. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 14 days before randomization.

    Note: If a single ECG shows a QTcF with an absolute value > 480 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

14. History of psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent.

15. Pregnant or breastfeeding females.

16. Inability to swallow tablets.

17. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe hypersensitivity to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.

18. Any other active malignancy at time of randomization or diagnosis of another malignancy within 2 years before randomization that requires active treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy.

5. STUDY ASSESSMENTS AND PROCEDURES

This protocol generally presents scheduled timelines for study procedures by abbreviated references to week (W) and day (D) (eg, W1D1, W3D1 etc.) relative to the date of the first dose of study treatment (defined as W1D1). Study W1D1 should occur within 3 days of randomization (W1D1 will be defined as the date of randomization for subjects who never receive study treatment).

All assessments for safety, efficacy (CT or MRI), and HRQOL assessments will be scheduled based on W1D1. Special accommodations during the global COVID-19 pandemic are described in Appendix M.

Unscheduled visits for safety evaluations are allowed at any time, and required in circumstances described herein.

See Appendix A for the schedule of assessments.

5.1. Pre-Treatment Period

Informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research. However, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization. At informed consent a study site representative will use the web-based IRT to register subjects. The IRT will assigned a unique subject identifier; subject identifiers are not to be re-assigned if a subject is determined to be ineligible, and subjects are to maintain their original identifier if re-screening is required or if the subject experiences a change in study site or investigator.

To determine subject eligibility as stipulated in Section 4, subjects will undergo required screening evaluations as outlined in Appendix A and described in Section 5.8.

Guidance for diagnosis of HCC in cirrhotic patients by imaging is provided in Section 5.8.6.1.

Qualifying screening assessments must be performed within 28 days before randomization unless otherwise stated (eg, certain lab values must be obtained closer to randomization). Eligibility criteria based on laboratory values should be based on central laboratory results. Exceptions for using local laboratory test results for eligibility determination include serum

pregnancy test (for females of child-bearing potential), urinalysis, repeat lab tests to confirm central lab test results, and laboratory tests which cannot be obtained from the central lab in time before the planned randomization date. Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening.

A subject who signs informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. Data on the following information will be collected for all screen failures:

- Informed consent information
- Failed inclusion/exclusion criteria
- Demographics
- SAEs

5.2. Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 2:1:1 fashion to receive cabozantinib in combination with atezolizumab or sorafenib or cabozantinib alone (Section 6.1.1). Subjects should receive their first dose of study treatment within 3 days after randomization.

While the subject is receiving study treatment the subject's clinical status is to be evaluated by an investigator at each clinic visit to confirm that the subject is suitable for continuing study treatment and to make timely decisions regarding the reduction, interruption, or restarting of study treatment. Clinical laboratory results from samples obtained during clinic visits and tumor assessments from imaging visits are to be reviewed by an investigator.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5.1). Treatment with study treatment may continue after radiographic progression per RECIST 1.1 as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment (see Section 5.8.6.3), that the potential benefit of continuing study treatment outweighs potential risks, and no other therapies are considered by the Investigator to be more appropriate. Subjects on the experimental arm (cabozantinib + atezolizumab) are allowed to discontinue one component of the study treatment but continue to receive the other. Escalation of cabozantinib from 40 mg qd to 60 mg qd in the experimental arm is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose

level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd. Crossover between treatment arms will not be allowed unless study transitions to the Crossover Phase.

Study completion is defined in Section 3.5.3.

Required safety assessments are to be performed on a schedule based on the date of the first dose (W1D1) and every 3 weeks (± 3 days) (ie, W4D1, W7D1, W10D1, etc). For subjects in the combination arm, required safety assessments may occur outside the protocol-defined windows due to safety-driven delays in atezolizumab administration and will not be considered protocol deviations as long as required safety assessments are performed at least every 3 weeks (± 3 days). See the CRF completion guidelines for instructions on how to enter study data in such circumstances. The following are the reminders:

- Doses of atezolizumab must not be given less than 19 days apart (see Section 6.2.4).
- Specific laboratory tests are required to be performed and evaluated within 72 hours prior to each administration of atezolizumab (see Section 5.8.5).
- The tumor assessment and HRQOL schedules are to be maintained relative to the date of first dose of study treatment (or randomization date for subjects never treated) irrespective of the dates of safety assessments.
- PK and biomarker sample collection schedules are per schedule of assessments (Appendix A and Appendix B).

Safety follow-up visits will be performed 30 (+14) days (FU-1) and approximately 100 days (± 14 days) (FU-2) after the date of the decision to permanently discontinue study treatment (see Section 8.4).

If study treatment is held due to AEs, investigators should perform additional safety assessments weekly (or more frequently as clinically indicated).

Radiographic tumor assessments should be performed as described in Section 5.8.6, and HRQOL assessments should be performed as described in Section 5.8.8. The schedule of assessments should be maintained regardless of whether study treatment is given, reduced, held or discontinued until a criterion for discontinuation of radiographic assessments is met (see Section 5.8.6.2).

In accordance with the ITT principle, HRQOL, radiographic tumor assessments, and survival follow-up are to be performed per protocol even for subjects randomized who never receive study treatment. For such subjects, W1D1 is defined as the date of randomization.

5.3. Crossover Phase

The study may transition to a Crossover Phase if the analysis of the primary endpoint of OS for the global ITT population (ie, not including subjects enrolled in the Mainland China Extension Phase) shows statistically significant and clinically meaningful evidence of improvement in favor of the experimental arm.

The Crossover Phase will only be implemented upon decision by the Sponsor and following any required discussion with regulatory authorities following review of the data. Crossover may be implemented independently and at different points in time for study sites and subjects in mainland China compared to other sites and subjects in the global study. If the decision is made to enter the Crossover Phase, study sites will have 8 weeks to determine eligibility and begin administration of crossover treatment (cabozantinib + atezolizumab combination) to eligible subjects randomized to the control arm (sorafenib) or the single-agent cabozantinib arm; subsequently no further crossover will be allowed.

- Subjects randomized to the sorafenib control arm or single-agent cabozantinib arm will have the option to crossover to receive the cabozantinib + atezolizumab combination if they meet predefined eligibility criteria.
- Subjects randomized to the cabozantinib + atezolizumab experimental arm who are still receiving study treatment and subjects randomized to the sorafenib control arm or single-agent cabozantinib arm who are still receiving study treatment and do not crossover to the experimental arm may continue on originally assigned study treatment until a criterion for protocol-defined discontinuation has been met.
- Subjects randomized to the cabozantinib + atezolizumab experimental arm who are in the post treatment period and subjects randomized to the sorafenib control arm or single-agent cabozantinib arm who do not crossover to cabozantinib + atezolizumab and are in the post-treatment period will continue with post treatment assessments.

The study is expected to have completed enrollment in the global enrollment phase at the time of transitioning to the Crossover Phase for subjects who enrolled in that phase, but accrual of subjects in the Mainland China Extension Phase may still be ongoing at that point. In the Crossover Phase safety assessments and efficacy assessments will continue as scheduled; PK, biomarker, HRQOL, and healthcare resource utilization assessments will be discontinued.

5.4. Post-Treatment Period

A first Post-Treatment Follow-up visit (FU-1) for safety evaluation (including subjects in the Maintenance Phase [below]) is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second Post-Treatment Follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Refer to Appendix A for a description of all assessments for the Post Treatment Follow-Up Visits. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix K.

Adverse events are to be documented and/or followed as described in Section 8.4.

Following treatment discontinuation each subject will continue to be followed for survival and receipt of subsequent anticancer therapy. The investigator (or designee) will make contact with the subject at least as frequently as every 12 weeks (± 14 days) after FU-2 until the subject expires, withdraws consent for such contacts, or the Sponsor decides to discontinue collection of these data for the study.

At each contact, the investigator (or designee) will determine if the subject died, and if so, record the date and cause of death as best can be determined. All efforts must be undertaken by the study sites to determine the date of death (or date subject last known alive at the time of a data cutoff). This may include, but not necessarily be limited to telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records. Receipt of subsequent nonprotocol anticancer therapy (NPACT) will also be collected during the Post-Treatment Period. If a subject is lost to follow-up, multiple attempts to contact the study subject or designee must be documented in the subject records.

HRQOL outcomes and radiographic tumor assessments will be collected regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment as described in Section 5.8.6.3. Consequently these assessments may be required in the Post-Treatment Period for some subjects.

5.5. Mainland China Extension Phase

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. The Pre-Treatment Period (Section 5.1), Treatment Period (Section 5.2), and

Post-Treatment Period (Section 5.4) of the study will be conducted in the same manner in the Mainland China Extension Phase as for subjects who were enrolled in the global enrollment phase.

5.6. Maintenance Phase/Treatment after Study Completion

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see Section 3.5.3). When sufficient data have been collected to adequately evaluate all study endpoints, subjects who continue study treatment may enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analysis required for regulatory purposes to have been completed. If a Crossover Phase has been implemented, the Maintenance Phase may not begin before the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last subject randomized to sorafenib or single-agent cabozantinib who crossed over to receive cabozantinib + atezolizumab. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.5.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B). The nature and frequency of these assessments are to be performed per institutional standard of care and guidance from the Sponsor. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs, and other reportable events (DILI, pregnancy, and medication errors with sequelae) is to continue per protocol (Section 8.2.2).

Further, the following AEs, whether serious or not, are to be reported using the same process as for reporting SAEs described in the protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse events of special interest (AESIs)
- Adverse events, whether serious or not, leading to study treatment discontinuation
- Adverse events, whether serious or not, leading to study treatment dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)

Study drug accountability is to continue as described in Section 6.5.

Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

5.7. Unscheduled Visits or Assessments

If the Investigator determines that a subject should be monitored more frequently or with additional laboratory assessments than indicated by the protocol-defined visit schedule, unscheduled visits or assessments are permitted. The laboratory assessments should be done by the central lab; however, if the results are needed immediately (eg, for AE management), they may be done by the local lab and the results forwarded to the management vendor for handling of local laboratory data. If study treatment is held, the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated during the intervening time between the last dose and the time drug is restarted to monitor subject safety and appropriateness for re-treatment with study treatment.

5.8. Procedure details

This section describes evaluations to be performed and items to be recorded or available on source documents. Data from some required evaluations may not be collected on study CRFs (see Section 16.4).

5.8.1. Demographics, Medical and Cancer History

Demographics at screening will include age at informed consent, medical and cancer history, surgical history, radiation therapy history, and other local anticancer treatment history including names of procedures, agents and administration dates. To ensure subject privacy, date of birth and subject initials will not be collected by the Sponsor.

5.8.2. Physical Examination

Physical examinations will include height (screening visit only), weight, performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examination will be conducted on W1D1 before first dose of study treatment and after randomization. Any ongoing/intercurrent condition

prior to first dose must be recorded as medical history. Significant new findings that begin or worsen after first dose must be recorded as AEs.

The ECOG performance status of the subject will be assessed during screening and at each scheduled safety assessment starting on W1D1. A table of performance status criteria is included in Appendix C for reference.

Refer to Appendix A for the schedule of physical examination and performance status assessments.

5.8.3. Vital Signs

Vital signs including 5-minute sitting BP, pulse, respiratory rate, and temperature will be assessed at screening, at all scheduled safety visits, and at all unscheduled visits if possible. On atezolizumab infusion days, vital signs should be assessed within 60 min prior to initiation of the infusion, and further vital sign assessment should be performed during and after the infusion as clinically indicated.

Refer to Appendix A for the schedule of these assessments.

5.8.4. Electrocardiograms

At screening and during the study, single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine QTcF. A QTcF ≤ 480 ms per single ECG within 14 days before randomization is required to demonstrate eligibility for study treatment. If at any time after the first dose of treatment the single ECG shows a QTcF with an absolute value > 500 ms or an increase from baseline of > 60 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 as the value assessed (see Section 6.6.2.1.15).

ECGs will be performed at the time points indicated in Appendix A.

Guidelines for management of corrected QT prolongation associated with cabozantinib and sorafenib are provided in Sections 6.6.2.1.15 and 6.6.2.3, respectively.

Abnormalities in the ECG that lead to a change in subject management (eg, dose reduced or interrupted, treatment discontinued, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be deemed AEs. If values meet criteria defining them as serious, they must be reported as SAEs (Section 8.2).

The Fridericia formula is depicted below for calculation of the corrected QT interval (QTcF).

$$QTcF = \frac{QT}{RR^{1/3}}$$

QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate)

5.8.5. Safety Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 2. The schedule for laboratory assessments is provided in Appendix A. Laboratory tests to establish eligibility must be done within 14 days before randomization unless otherwise stated (Appendix A).

Central laboratory assessments: Hematology, serum chemistry, coagulation, UPCR including components, hepatitis, and thyroid function tests are to be performed by a central laboratory, including laboratory assessments obtained at unscheduled visits whenever possible. All central safety laboratory results will be provided to the Investigator.

Eligibility criteria based on laboratory values should be based on central laboratory results. Exceptions for using local laboratory test results for eligibility determination include serum pregnancy test, urinalysis, certain laboratory values that are required to be repeated closer to randomization, and laboratory tests which cannot be obtained from the central lab in time before the planned randomization date (see Appendix A).

Local laboratory assessments: Routine (dipstick) analysis, microscopic urine examination, and serum/urine pregnancy tests (for females of child-bearing potential) are to be done by local laboratory. Results or status from these tests will be recorded on CRFs and will not be submitted to the study local laboratory management vendor.

24-hour urine protein tests, at any scheduled or unscheduled visit, are to be done by local laboratory and the lab results forwarded to the study local laboratory management vendor.

After randomization, local laboratory analyses may be employed if the results are required by the Investigator in a rapid timeframe (eg, needed for making rapid treatment decision or monitoring for AEs, SAEs).

Guidance on central vs local clinical laboratory analyses for post-randomization safety laboratory samples:

- If possible, the serum chemistry, hematology, coagulation, and thyroid function tests are to be done via central laboratory, but may be done locally if central laboratory testing is not feasible in a timely manner.

    - Serum chemistry, hematology, and coagulation tests (specific parameters listed in Table 2) must be performed, and results must be reviewed within 72 hours prior to atezolizumab administration.

    - If the subject has symptoms indicative of a thyroid function disorder, thyroid function test results are to be reviewed prior to administering atezolizumab.

Urinalysis is to be done locally. Local test results are to be submitted to the local laboratory management vendor as described in Table 2.

    - Urinalysis must be performed, and results must be reviewed within 72 hours prior to atezolizumab administration.

All-local laboratory results must be forwarded to the study local laboratory management vendor if performed in lieu of the central laboratory assessment at any scheduled or unscheduled visit.

Other specific laboratory test information:

- To confirm suitability for treatment after randomization, 12-lead ECG and all laboratory tests (except for pregnancy test) must be performed within 14 days prior to administering the first dose of study treatment. These assessments do not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration) since the most recent assessment performed to establish eligibility and suitability for study treatment. If any of these tests are performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

- A serum pregnancy test must be repeated before dosing on W1D1 unless a pregnancy evaluation was done during screening within 7 days prior to W1D1.

- Follicle stimulating hormone (FSH). For women under the age of 55 years to confirm menopause as needed during the screening period.

- Hepatitis B surface antigen and core antibody (with reflex testing of hepatitis B DNA if either antigen or core antibody is positive; hepatitis B DNA testing is mandatory in mainland China), and Hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive) will be assessed at screening by central laboratory. If central laboratory results are not

available at the time of randomization, local laboratory results may be used with Sponsor approval.

- HIV test will be performed at screening if required by local regulation. Results from this test do not need to be forwarded to the study local laboratory management vendor.

- In addition to the safety laboratory assessments, tumor marker (AFP) will be assessed by the central lab at screening, predose on W1D1, and after first dose of study treatment as described in the schedule of assessments (Appendix A). These assessments will not be used to determine PD in this study.

Table 2: Laboratory Panels

Central Laboratory

If performed by local laboratory submit results to study local laboratory management vendor

Hematology

- White blood cell (WBC) count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)
- hematocrit
- platelet count
- red blood cell count
- hemoglobin

Coagulation

- prothrombin time (PT)/International Normalized Ratio (INR)
- partial thromboplastin time (PTT)

Thyroid function

- thyroid-stimulating hormone (TSH)
- Free thyroxine (FT4; required at screening; after screening only if TSH is outside normal range)

Other parameters

- Follicle Stimulating Hormone (FSH)[a]
- Alpha-fetoprotein (AFP)

Serum Chemistry

- albumin
- total alkaline phosphatase (ALP)
- amylase
- alanine amino transferase (ALT)
- aspartate amino transferase (AST)
- blood urea nitrogen (BUN)
- corrected calcium
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin (including unconjugated and conjugated fractions)
- total protein

Urine Chemistry

- Protein (spot urine; fully quantitative)
- Creatinine (spot urine; fully quantitative)
- Urine protein/creatinine ratio (UPCR; spot urine)

Virology

- Hepatitis B surface antigen, Hepatitis B core antibody, (with reflex testing of hepatitis B DNA if either antigen or core antibody is positive [hepatitis B DNA mandatory in mainland China])
- Hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive)

Local Laboratory

Submit only 24-hour urine protein test results to study local laboratory management vendor

Urinalysis

(Dipstick or Routine per Institutional Standard)

- pH
- specific gravity
- ketones
- protein
- glucose
- nitrite
- urobilinogen
- leukocyte esterase
- blood

Microscopic Urine Examination

- Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated

Urine Chemistry

- 24-hour urine protein: perform at the discretion of the investigator based on increases in UPCR from routine assessments

Pregnancy Blood Test (prior to first dose)

- β-human chorionic gonadotropin (β-HCG)

Pregnancy Urine or Blood Test (after first dose of study treatment)

- β-human chorionic gonadotropin (β-HCG)

Virology

- HIV test (if mandated by local regulation)

[a] For women under the age of 55 years to confirm menopause as needed.

Table 3: Estimation of the Creatinine Clearance by Cockcroft and Gault

Based on serum creatinine in conventional units (mg/dL) • Males: (140 – age) × weight (kg)/(serum creatinine × 72) • Females: [(140 – age) × weight (kg)/(serum creatinine × 72)] × 0.85
Based on serum creatinine in SI units (µmol/L) • Males: [(140 – age) × weight (kg)/(serum creatinine)] × 1.23 • Females: [(140 – age) × weight (kg)/(serum creatinine)] × 1.04

Abnormalities in any clinical laboratory test (including tests not required per protocol) that lead to a change in subject management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and should be reported as AEs. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (with associated laboratory values) needs to be reported as an SAE (see Section 8.2).

5.8.6. Tumor Assessments

5.8.6.1. Diagnosis of HCC in Cirrhotic Patients by Imaging for Study Eligibility

Clinical diagnosis of HCC by multiphase imaging using CT or MRI in subjects with cirrhosis according to AASLD or EASL HCC guidelines is acceptable for study eligibility. Diagnostic imaging hallmarks of HCC include arterial phase enhancement, tumor size, washout, enhancing capsule, and threshold growth. If the subject does not have cirrhosis or these imaging criteria cannot be assessed or are not met, histological or cytological diagnosis of HCC is required for study participation. Ultrasound, angiography, fluorodeoxyglucose (FDG)-positron emission tomography (PET), or AFP cannot be used for clinical diagnosis of HCC. Accreditation for HCC diagnostic imaging, as described in the amended study imaging manual, is required before a site can enroll subjects diagnosed with HCC via imaging alone. Diagnostic scans may be used for screening if they meet the criteria described in Section 5.8.6.2. For detailed guidance regarding diagnosis of HCC by imaging refer to the amended study imaging manual.

5.8.6.2. Routine Tumor Assessment

Radiographic response and disease progression will be determined using RECIST version 1.1 (Appendix E). For the purpose of determination of the radiographic study endpoints, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments will be promptly sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions. Sites will be provided with instructions for how images should be collected and submitted to the BIRC. Study staff shall ensure that no images contain personal data as defined by applicable local, regional, and international laws and regulations.

Radiographic tumor assessments will include the following:

1. **Chest / Abdomen / Pelvis (CAP):** CT of CAP or CT chest and MRI abdomen/pelvis will be performed in all subjects at screening (prior to randomization). Tumor assessments after randomization should be performed every 6 weeks (± 7 days) through Week 49. After Week 49, these assessments will be performed every 12 weeks (± 7 days). CT/MRI of the CAP should include a noncontrast study of at least the liver followed by contrast with triphasic CT imaging of the liver or liver MRI with gadolinium enhanced imaging including triphasic liver.

2. **Other sites**: All other known or suspected sites of disease, including in the brain or bone, are to be imaged by CT/MRI at screening (prior to randomization). Any lesions identified, including bone lesions with a soft tissue component, are to be followed at subsequent tumor assessments as described for CAP above using the same modality as at screening. New suspected lesion sites identified after randomization, including suspected sites of bone or brain lesions, should be assessed by CT/MRI. MRI is the preferred method for brain lesion assessment. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 8 weeks before randomization. Subjects without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.)

If there is clinical concern regarding the administration of any contrast agent, then tumor assessments for the liver should be performed by MRI with non-contrast CT of the chest. If at a follow up imaging time point the use of contrast is prohibited (eg, due to acquired impaired renal function) then the same modality should be used without contrast.

Tumor assessments should continue on the protocol-defined schedule regardless of whether study treatment is given, reduced, held or discontinued until a criterion for ending radiographic assessments is met. The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization. Radiographic tumor assessments are to continue until the later of Investigator-determined radiographic progression per RECIST 1.1 or study treatment is permanently discontinued. Further guidance for continuation or termination of tumor assessments based on subject status is provided in Table 4.

Table 4: Criteria for Discontinuing Radiographic Assessments

Subject Status		Action with Radiographic Assessments
Study Treatment Permanently Discontinued?	**Investigator-Assessed rPD per RECIST 1.1 Reached or Initiation of Systemic NPACT?**	
No	No	Continue assessments
No	Yes[a]	Continue assessments (ie, Investigator deems the clinical benefit of continued study drug treatment outweighs the potential risks)
Yes	No	Continue assessments
Yes	Yes	Discontinue assessments

NPACT, non-protocol anticancer therapy; rPD, radiographic progressive disease; RECIST 1.1, Response Evaluation Criteria for Solid Tumors version 1.1.

[a] Investigator-assessed rPD only. Receipt of NPACT is a requirement for study treatment discontinuation (see Section 3.5.1).

Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the Investigator does not necessarily warrant discontinuation of tumor assessments or study treatment.

Refer to Appendix A for the schedule for these assessments.

5.8.6.3. Confirmation of Tumor Response/Progression and Treatment beyond Progression

For subjects with an overall response of PR or CR per RECIST 1.1 by investigator at a given time point, a repeat assessment is to be performed no fewer than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled tumor assessment.

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have tumor measurement outcomes confirmed by the Investigator after the initial Investigator-assessed PD criteria were met. This is to be performed no later than the next scheduled tumor assessment. Continuation of study treatment after confirmatory tumor imaging for PD is allowed for subjects who meet all the following criteria:

- Clinical benefit per Investigator judgment
- ECOG performance status of 0 or 1
- Absence of unmanageable treatment-related AEs
- Tumor status does not require urgent alternative medical interventions (eg, central nervous system [CNS] metastases)

Subjects who are eligible to continue with study treatment must provide written informed consent.

Reasons for treatment discontinuation are provided in Section 3.5.1. For subjects who continue treatment after the documentation of radiographic PD, regularly scheduled imaging will continue until treatment discontinuation.

5.8.6.4. Blinded Independent Radiology Committee

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease must be sent to the BIRC preferably in original Digital Imaging and Communications in Medicine (DICOM) format (as detailed in the Site-specific Imaging Core Manual). The BIRC will evaluate prior radiation history for the purpose of valid identification of target lesions and all images in a central and independent fashion as further described in Section 12.4. Electronic transfer of scan files (via FTP, HTTP, or similar means) is preferred, although transfer on physical media (such as DVDs or CDs) is acceptable. For digital media, each disk should contain one time point for one subject. The site is expected to maintain a copy of digital data for the retention period applicable to the

protocol, GCPs, and federal, international and/or state legal and medical requirements. The Sponsor and or designee will retain the media for the life of the study.

5.8.7. Tumor Marker Assessment

Tumor marker samples (AFP) will be collected at screening, predose on W1D1, and after first dose of study treatment as described in the schedule of assessments (Appendix A). The tumor marker assessments will not be used to determine PD in this study. The samples will be analyzed by a central laboratory.

5.8.8. Health-related Quality of Life Assessments

Health-related QOL assessments will be performed using the EuroQol Health questionnaire instruments EQ-5D-5L (Appendix L). This is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog scale (VAS). The utility data generated from EQ-5D-5L are recommended for and commonly used in cost effectiveness analysis. The first assessment will be performed within 14 days prior to randomization. Assessment will be collected every 6 weeks after W1D1 (eg, W7D1, W13D1, etc). For randomized subjects who never receive study treatment, W1D1 is defined as the date of randomization. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or the study meets its primary endpoints. Consequently these assessments may be required in the Post-Treatment Period for some subjects (Appendix A).

Subjects are to complete the questionnaires prior to each clinic visit or, if completed on the day of the visit, before seeing the study site personnel. If a clinic visit is not possible subjects should complete the questionnaires as per schedule and return it to the site either during the next visit or should send it to the site by fax or postal mail. Ideally, study subjects should not receive any information about their most recent medical results prior to completing the questionnaires in order to ensure that their reporting is not influenced by such information when completing the questionnaires. At clinic visits, questionnaires should be carefully reviewed by the study staff at the site for completeness.

Subjects who are not compliant with completing the questionnaires should be reminded by the Investigator that these reports are an essential part of the study and timely completion is required.

Every effort should be made by the study site to retrieve all HRQOL questionnaires including the assessment following radiographic progression or discontinuation of study treatment, and to keep them at the site as source documentation.

Translated copies of the EQ-5D-5L questionnaires, if required, and instructions for filling them out will be provided to each study site in a separate study manual. HRQOL assessments will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

5.8.9. Healthcare Resource Utilization

Healthcare resource utilization parameters will be collected from randomization through the 100-Day Post-Treatment Follow-up Visit (FU-2). These include hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions. These data will not be collected in the Maintenance Phase.

5.8.10. Pharmacokinetic Assessments

Blood samples will be obtained from all subjects in the experimental arm (cabozantinib + atezolizumab) and the single-agent cabozantinib arm (60 mg) for cabozantinib PK. Samples will be collected for plasma cabozantinib concentration measurement predose on W1D1, W4D1, W7D1, W10D1, and W13D1. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib in this population.

Blood samples will be obtained from all subjects in the experimental arm for atezolizumab PK. Serum samples will be collected predose on W1D1, W4D1, W7D1, W10D1, W13D1, and at the Post-Treatment Follow-up visits (FU-1 and FU-2). The results may be used to confirm exposure to atezolizumab.

Collection of PK samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

5.8.11. Immunogenicity Assessments

Blood samples will be obtained from all subjects in the experimental arm (cabozantinib + atezolizumab) for immunogenicity assessment predose on W1D1, W13D1, W25D1, and at the Post-Treatment Follow-up visits (FU-1 and FU-2). Collection of immunogenicity samples may be halted early, or sampling frequency may be reduced at the discretion of the Sponsor.

5.8.12. Biomarker Assessments

Peripheral blood samples will be obtained as specified in Appendix A. Archival tumor tissue (most recently obtained) will be provided, if available. If archival tissue and histological/cytological confirmation of disease are not available, a tumor biopsy may be collected during screening with subject consent. An optional tumor biopsy may be collected approximately

6 weeks after the first dose of study treatment; other time points may be acceptable provided the tumor sample is collected prior to progressive disease. Treatment with cabozantinib or sorafenib must be interrupted for at least 5 days before optional tumor biopsies are performed and may not be reinitiated until complete wound healing has occurred (at least 10 days). Exploratory analyses may include, but may not be limited to, the following:

- PD-L1, MET, and other relevant biomarkers in tumor specimens for association with clinical outcomes
- Immune cell infiltration and mutational load assessment in tumor specimens for association with clinical outcome
- Circulating immune cells in peripheral blood
- Blood biomarkers (ie, cytokines/chemokines, VEGF)
- Cell and/or plasma pharmacogenomics (eg, circulating tumor DNA [ctDNA])

Collection of biomarker samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor. Some biomarker samples may only be collected at selected sites (see the study laboratory manual for details).

The required blood samples will be used to study plasma, serum, and cellular biomarkers. The most recent archival/fresh tumor biopsy and optional on-treatment tumor tissue samples will be used to evaluate changes in biomarker expression and genetic/genomic alterations. The analyses will help identify biomarkers that are predictive of response to the study drugs, and may help improve understanding of tumor development, tumor microenvironment, and effects on peripheral immune activity for the study indication. Analyses may include, but may not be limited to, sequencing of DNA and/or RNA from tissue and/or blood (plasma) to look for genetic/genomic alterations (eg, mutations, copy number variation, mutational burden), immunohistochemistry (IHC) assessment of biomarker levels in tissue (eg, MET, PD-L1), and immune cell profiling by fluorescence-activated cell sorting (FACS) analyses. Immune cell profiling by FACS may be conducted at selected sites. These studies may use conventional as well as novel technology or methodology. The goal is to correlate modulation of these putative biomarkers to clinical outcome as a consequence of study treatment.

In addition, pharmacogenetic analyses involving single nucleotide polymorphism (SNP) genotyping may be performed in order to correlate variations in subject genotype with the safety/ tolerability, PK, and/or pharmacodynamics (biomarker analyses) of cabozantinib and/or atezolizumab.

The biomarker assessment samples may also be used for diagnostic assay development related to study drug and for the discovery of biomarkers that may prove to be valuable surrogates for clinical response and to understanding the underlying mechanisms of the disease.

5.8.13. Overall Survival

Overall survival will be assessed every 12 weeks (± 14 days) after the FU-2, which occurs 100 days (±14 days) after discontinuation of study treatment. Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data. Receipt of subsequent NPACT will also be collected during follow-up contacts. If a subject withdraws consent to participate in the study, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations. These assessments are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

5.9. Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the requirements or procedures of this protocol or from ICH GCP. Efforts should be made to limit deviations. The Investigator is responsible for promptly reporting protocol deviations as applicable to their IRB/EC and/or to the Sponsor per IRB/EC policy. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety, and determine if additional reports or actions are required. For important or repeated protocol deviations, additional action may include site re-training, hold or closure of enrollment, and/or site termination.

6. TREATMENTS

6.1. Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations. Special accommodations during the global COVID-19 pandemic are described in Appendix M.

6.1.1. Study Treatment

6.1.1.1. Cabozantinib (XL184) Tablets

The Sponsor will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 60-mg and 20-mg yellow film-coated tablets. The 60-mg tablets are oval and the 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 5.

Table 5: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib Drug Substance (CCI drug load as free base)	Active Ingredient	CCI
Microcrystalline Cellulose (Avicel® PH-102)	Filler	
Lactose Anhydrous (60M)	Filler	
Hydroxypropyl Cellulose (EXF)	Binder	
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	
Colloidal Silicon Dioxide	Glidant	
Magnesium Stearate	Lubricant	
CCI Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	

All study medication will be stored at controlled room temperature and inventoried according to applicable regulations. Further information on storage and handling will be provided in the pharmacy manual.

6.1.1.2. Atezolizumab

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody (non-glycosylated IgG1 kappa immunoglobulin) produced in Chinese hamster ovary cells with a calculated molecular mass of 145 kDa.

The Sponsor will provide each investigator with adequate supplies of atezolizumab, which will be supplied as a 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in single-dose vials. Atezolizumab solution contains the following inactive ingredients: glacial acetic acid, L-histidine, sucrose, and polysorbate 20. Refer to the package insert (or the local label) and the pharmacy manual for additional information and instructions for preparing atezolizumab for infusion. Commercially sourced solution used as diluent (0.9% NaCl) should be obtained by investigative sites according to local regulations.

6.1.2. Sorafenib

Sorafenib is a kinase inhibitor indicated for the treatment of HCC. The sponsor will provide each investigator with adequate supplies of commercially obtained sorafenib. Sorafenib tablets contain the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red. Refer to the most current local prescribing information appropriate to the respective site location.

6.2. Treatment Schedule of Administration

6.2.1. Experimental Arm: Cabozantinib in Combination with Atezolizumab

Cabozantinib at a dose of 40 mg (2 × 20 mg tablets) will be administered orally, once daily. Atezolizumab will be administered at a standard dosing regimen of 1200 mg as an IV infusion once every 3 weeks.

Subjects will receive study treatment with cabozantinib and atezolizumab as long as they continue to experience clinical benefit as assessed by the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5.1). Subjects are allowed to discontinue one component of the study treatment but continue to receive the other; investigators are encouraged to consult with the Sponsor before doing so.

Escalation of cabozantinib from 40 mg qd to 60 mg qd is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd.

For guidance on dose modifications, interruptions, delays, or discontinuations due to AEs, refer to Sections 6.6.1 and 6.6.2.

6.2.2. Control Arm: Sorafenib

The recommended dose of sorafenib in adults is 400 mg (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg). For detailed guidance, refer to the most current local prescribing information appropriate to the respective site location.

6.2.3. Single-Agent Cabozantinib Arm: Cabozantinib

The dose of cabozantinib on the single-agent cabozantinib arm is 60 mg orally, once daily. Subjects will receive study treatment with cabozantinib as long as they continue to experience clinical benefit as assessed by the investigator (see Section 5.8.6.3) or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5.1). For guidance on dose modifications, interruptions, delays, re-escalation after dose reductions, or discontinuations due to AEs, refer to the Section 6.6.1.

6.2.4. Study Drug Administration on Week 1 Day 1 (W1D1)

The first dose of study treatment should occur as soon as possible after randomization. The date of the first dose of study treatment is defined as W1D1. The first doses of all study treatments are to be administered at the clinic.

Cabozantinib:

For subjects receiving cabozantinib (experimental arm and single-agent cabozantinib arm), subjects will fast (with the exception of water) for at least 2 hours before receiving cabozantinib. Upon completion of the 2-hour fast, the subject will receive the oral dose of cabozantinib with a minimum of 8 oz (240 mL) of water in the clinic and then the subject will continue to fast for 1 hour while under observation at the clinic. For subjects on the experimental arm (cabozantinib and atezolizumab), atezolizumab is to be administered first. For cabozantinib dosing on subsequent dosing days refer to Section 6.2.5.

Atezolizumab:

Doses of atezolizumab will be administered intravenously at the clinic by infusion every 3 weeks (± 2 days).

The infusion of atezolizumab (1200 mg fixed dose) will be prepared according to local prescribing information or the pharmacy manual. The IV administration of atezolizumab can only occur in a clinical setting with staff experienced in managing of infusion-related reactions (IRRs) and with access to emergency services. The initial IV infusion of atezolizumab will be given over 60 min (± 15 min) without premedication for potential IRRs or CRS. Subsequent IV infusions may be given over 30 min (± 10 min) if the initial infusion is tolerated. Premedication

for IRRs or CRS is allowed after the initial infusion. No bolus or IV push of atezolizumab is allowed. Dose delays will be allowed for toxicities suspected to be due to atezolizumab administration. Atezolizumab infusion requirements and guidance are summarized in Table 6.

Table 6: Atezolizumab Infusion Requirements and Guidance

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

CRS, cytokine release syndrome; IRR, infusion-related reaction.

After the IV administration of the first dose of atezolizumab in the clinic, the subject will wait for at least 1 hour before taking cabozantinib. If the subject develops an infusion reaction or CRS, the oral administration of cabozantinib will be delayed or interrupted until the subject has recovered and the Investigator believes that it is safe to administer cabozantinib. For management of IRRs or CRS refer to Appendix G.

If the first dose of atezolizumab cannot be given for any reason, no oral treatment with cabozantinib is to be initiated.

Sorafenib:

On the first day subjects are to fast (with the exception of water) for at least 2 hours before receiving sorafenib. After the 2-hour fast, the subject are to take the 400 mg oral dose of sorafenib with a glass of water in the clinic with no food intake for one more hour post-dose while under observation at the clinic to monitor for potential AEs. Subsequent doses will be self-administered at home (Section 6.2.6). Any unused study treatment must be returned to the study site for drug accountability and disposal.

Refer to the current sorafenib label appropriate to the respective site location for additional details regarding recent major label changes, indication and usage, dosage and administration, dose modifications, contraindications, warnings and precautions, adverse reactions, drug interactions, and use in specific populations.

6.2.5. Cabozantinib Administration outside the Clinic

The subject should take cabozantinib outside the clinic at approximately the same time every day, preferentially before going to bed, and should adhere to the fasting requirements described in this section.

Subjects are to fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose. After the 2-hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no food intake for one more hour post-dose. If the subject's schedule requires taking cabozantinib during the day, the subject is to be instructed to follow the same fasting recommendations.

Tablets should not be crushed or chewed. Grapefruit and Seville oranges (and products made from them) should be avoided while being treated with cabozantinib.

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

Any unused study treatment must be returned to the study site for drug accountability and disposal.

6.2.6. Sorafenib Administration outside the clinic

Sorafenib should be taken orally twice daily at the same time each day. Sorafenib should be taken either without food or with a low-fat or moderate fat meal. If a subject intends to have a high fat meal, sorafenib should be taken at least 1 hour before or 2 hours after the meal. Sorafenib tablets should be swallowed whole with a glass of water. Subjects should be instructed that if a dose of sorafenib is missed, the next dose should be taken at the regularly scheduled time, and the subject should not double the dose. Refer to the current sorafenib label appropriate to the respective site location for additional details regarding dosage and administration.

6.3. Treatment after Study Completion

After study completion (see Section 3.5.3), subjects who continue to demonstrate clinical benefit may be eligible to receive Exelixis-supplied study treatment for the maximum treatment duration specified in Section 6.2 during the Maintenance Phase. Alternatively, study treatment may be provided via a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of Exelixis.

Exelixis reserves the right to terminate access to Exelixis-supplied study treatment if any of the following occur:

a) The study is terminated due to safety concerns.

b) The development of atezolizumab or cabozantinib is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives (eg, the null hypothesis is not rejected for the primary endpoint of OS).

c) The participant can obtain medication from a government-sponsored or private health program.

In all cases Exelixis will follow local regulations. Exelixis will work with study investigators to act in the best interest of subjects.

6.4. Compliance

Subject compliance with outpatient study treatment will be assessed by the site using drug dispensing and return records, infusion logs, progress notes about dose reductions/interruptions, and subject interview. These data will not be directly recorded in the CRF; rather, the CRF will capture infusion details and, for oral study treatment, intervals of constant dose and reasons for changes in dose level (eg, a new record completed each time dose level changes, including periods where no dose was taken, and the reason for a dose level change).

6.5. Study Treatment 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 when 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. Drug accountability will be performed periodically by the Sponsor or designee at interim monitoring visits. To satisfy regulatory requirements, at the time of site closure all unused study treatment will undergo final reconciliation and be destroyed according to applicable state, federal, and local regulations.

6.6. Safety Considerations

6.6.1. Management of AEs with Dose Reductions and/or Dose Interruptions

Subjects will be monitored for SAEs from the time of signing informed consent and for nonserious AEs from first dose of study treatment. Monitoring continues through 30 days (100 days for AESIs [Table 31] regardless of seriousness and for unrelated SAEs) after the date of the decision to permanently discontinue all study treatment (defined as the later of the date of the decision to discontinue all study treatment or the date of the last dose of any study treatment). Longer monitoring periods are required for related SAEs and certain other events as described in Section 8.4. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix K. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be graded by the Investigator according to CTCAE v5.

The following should be taken into consideration in decisions regarding management for treatment-related side effects:

- Cabozantinib and atezolizumab have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs in the experimental arm which can be clearly attributed to either cabozantinib or atezolizumab, independent dose modification for either agent is allowed.
    - Examples of VEGFR-TKI associated AEs caused by cabozantinib are hypertension and hand-foot syndrome.
    - Examples of AESIs caused by atezolizumab are pneumonitis and endocrinopathies.

  For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications of both agents per the discretion of the Investigator. Examples of overlapping AEs are diarrhea and transaminase increases.

- As a general approach all AEs should be managed with supportive care including both pharmacological and non-pharmacological treatments according to consensus management guidelines at the earliest signs of toxicity considered related to study treatment.

- Study treatment may be continued for mild AEs if appropriate supportive care has been initiated to ameliorate symptoms. Should this be ineffective and toxicities become

unacceptable, dose modifications of study treatment should be considered to prevent worsening of toxicity. Moderate to severe AEs usually require dose modifications including dose reductions and/or interruptions.

- Dose interruptions of cabozantinib or atezolizumab for AEs may occur at any time and independently at the discretion of the Investigator. If both study treatments in the experimental arm or sorafenib in the comparator arm are interrupted for more than 12 weeks, treatment should be discontinued unless approved by the Sponsor. Dose interruptions of sorafenib for AEs may also occur at any time at the discretion of the Investigator.

- Subjects on the experimental arm (cabozantinib + atezolizumab) will be allowed to discontinue one component of the study treatment but continue to receive the other; the Investigator is encouraged to discuss such circumstances with the Sponsor.

Cabozantinib:

- The assigned dose for cabozantinib in the experimental combination arm is 40 mg qd. Escalation of cabozantinib from 40 mg qd to 60 mg qd is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 mg qd to 60 mg qd. The assigned dose for cabozantinib in the single-agent cabozantinib arm is 60 mg qd.

- Two dose reduction levels of cabozantinib (20 mg daily, and 20 mg every other day [qod]) are permitted on the experimental combination arm (see Table 7).
  Note: Subjects who have their dose escalated to 60 mg on the experimental arm would be permitted to reduce dose back to 40 mg before further reduction to lower dose levels.

- Two dose reduction levels of cabozantinib (40 mg daily, 20 mg daily) are permitted on the single-agent cabozantinib arm (see Table 7).

- Dose modification criteria for treatment-related AEs of cabozantinib are shown in Table 8.

- Dose reinstitution and reescalation after dose interruptions and/or reductions:

  - If the subject recovers from his or her toxicities to ≤ Grade 1 per CTCAE v5 or to the baseline value (or lower) and the AE 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) and the AE was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose (see Table 8). Subjects who initiated treatment with cabozantinib at 40 mg and experience a possibly related AE of Grade 1 or 2 severity may be restarted with no dose change after recovery of the toxicities to ≤ Grade 1 or to the baseline value (or lower) if appropriate supportive care can prevent or minimize the risk of the AE.

- Subjects receiving a dose of 20 mg qod on the experimental combination arm (20 mg qd on the single-agent cabozantinib arm) who have cabozantinib interrupted may be restarted at the same dose if deemed safe at the discretion of the Investigator. Subjects unable to tolerate a dose of 20 mg qod (20 mg qd on the single-agent cabozantinib arm) must discontinue cabozantinib.

- Reescalation to the previous dose 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 reescalation is not allowed following a cabozantinib-related dose reduction for Grade 4 AEs affecting major organs (eg, CNS, cardiac, hepatic, renal, pulmonary, GI).

- Guidelines for the management of specific AEs of cabozantinib such as 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 are provided in Section 6.6.2.1.

Table 7: Dose Levels of Cabozantinib (Oral Dosing)

Assigned Starting Dose	First Dose Level Reduction	Second Dose Level Reduction	Third Dose Level Reduction
40 mg daily (qd)[a] (Experimental arm)	20 mg daily (qd)	20 mg every other day (qod)[b]	No dose reduction permitted
60 mg daily (qd) (Single-agent cabozantinib arm)	40 mg daily (qd)	20 mg daily (qd)[c]	No dose reduction permitted

[a] Subjects who have their dose escalated to 60 mg on the experimental arm would be permitted to reduce dose back to 40 mg before further reduction to lower dose levels.
[b] Cabozantinib will be discontinued on the experimental if a dose of 20-mg cabozantinib every other day is not tolerated.
[c] Cabozantinib will be discontinued on the single-agent cabozantinib arm if a qd dose of 20 mg cabozantinib is not tolerated

Table 8: Dose Modifications for Cabozantinib-Related AEs

CTCAE v5 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib at the current dose level with supportive care.
Grade 2 AEs which are **intolerable and cannot be adequately managed**	Cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose interruptions 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 of cabozantinib and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib must be interrupted immediately. In general, cabozantinib should be discontinued unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction of cabozantinib following recovery to Grade 1 (or baseline) and optimal medical care Sponsor must be contacted to discuss treatment continuation upon resolution of AEs.

AE, adverse event.

Note: Cabozantinib dose modification criteria for specific medical conditions are provided in Section 6.6.2.1.

Atezolizumab:

- The assigned dose for atezolizumab is 1200 mg IV every 3 weeks. Infusion will occur every three weeks (± 2 days).
- Dose delays are allowed for atezolizumab (see Table 9), but dose reductions are not allowed.
- Dose modification criteria for irAEs and other AESIs and for guidance on reinstituting atezolizumab are shown in Table 10.
- If corticosteroids are initiated for treatment of irAEs, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Guidelines for the management of IRRs and CRS, irAEs for atezolizumab (ie, pneumonitis, hepatitis, diarrhea/colitis, myocarditis, endocrinopathies including hypophysitis, and infection) and other AESIs are provided in Section 6.6.2.2.

Table 9: Dose Interruptions of Atezolizumab

Assigned dose	Dose Interruptions
1200-mg atezolizumab IV q3w	At any time to manage unacceptable AESIs

AESI, adverse events of special interest; q3w, once every 3 weeks;

Table 10: Dose Modifications for Atezolizumab-Associated Adverse Events

CTCAE v5 Grade	Recommended Management
Grade 1 immune-mediated myelitis* Grade 1 pericarditis** Grade 2 myocarditis Grade 1[a] - 2 pneumonitis Grade 2 nephritis Transaminases (ALT or AST): • Increases to between > 3 × ULN and ≤ 10 × ULN (from baseline values ≤ ULN), or • Increases to between > 5 × ULN and ≤ 10 × ULN (from baseline values between > ULN and ≤ 3 × ULN), or • Increases to between > 8 × ULN and ≤ 10 × ULN (from baseline values between > 3 × ULN and ≤ 5 × ULN)	Delay treatment with atezolizumab Treatment may be resumed in subjects following recovery to Grade 0-1 * Continue atezolizumab unless symptoms worsen or do not improve. ** Withhold treatment with atezolizumab and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

CTCAE v5 Grade	Recommended Management
Grade 2 immune-mediated neuropathy (any cranial nerve disorder, including facial paresis, should be managed as per Grade 2 guidelines)*** Grade 2 or 3 diarrhea or colitis Grade 2 or 3 myositis Symptomatic adrenal insufficiency, hypothyroidism, or hyperthyroidism; Grade 2 or 3 hypophysitis; or Grade 3 or 4 hyperglycemia Grade 2 ocular inflammatory toxicity Grade 2 or 3 pancreatitis or Grade 3 or 4 increases in amylase or lipase levels Grade 3 or 4 infection Grade 2 infusion-related reactions or cytokine release syndrome Grade 3 rash Suspected Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade) Other Grade 2 or 3 atezolizumab-associated AEs	Delay treatment with atezolizumab Treatment may be resumed in subjects following recovery to Grade 0-1. *** For general immune-related neuropathy, if the event resolves to Grade 1 or better, resume atezolizumab. For facial paresis, if event resolves fully, resume atezolizumab; if event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab.
Grade 2 - 4 immune-mediated myelitis Grade 3 or 4 immune-mediated neuropathy, including facial paresis Grade 2 - 4 myocarditis Grade 4 myositis and/or recurrent Grade 3 myositis Grade 3 or 4 pneumonitis Grade 3 or 4 nephritis AST or ALT > 10 × ULN or total bilirubin > 3 × ULN Grade 4 diarrhea or colitis Grade 4 hypophysitis and/or recurrent hypophysitis Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades) Grade 3 or 4 ocular inflammatory toxicity Grade 4, or recurrent Grade 2 or 3, immune-mediated pancreatitis	Permanently discontinue atezolizumab

CTCAE v5 Grade	Recommended Management
Grade 3 or 4 infusion-related reactions or cytokine release syndrome Grade 4 rash Confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	
Other Grade 4 or recurrent Grade 3 atezolizumab-associated AEs	Permanently discontinue atezolizumab

AE, adverse event; AESI, adverse events of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; ULN, upper limit of normal.

Note: Additional information for atezolizumab dose modification criteria and treatment recommendations for irAEs, infusion reactions, and other AESIs are provided in Section 6.6.2.2.

[a] Consider interrupting atezolizumab for Grade 1 pneumonitis.

[b] 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 investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Sorafenib:

- The assigned dose for sorafenib is 400 mg twice daily.
- When dose reduction is necessary, the sorafenib dose may be reduced to 400 mg once daily (qd). If additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (qod).

For additional details on management guidance of AEs refer to the most current sorafenib prescribing information appropriate to the respective site location.

6.6.2. Warnings, Precautions, Guidelines for Management of Adverse Events

Management of severe or intolerable adverse reactions may require temporary dose reductions and/or interruptions for cabozantinib and sorafenib, and/or dose delays of atezolizumab therapy.

6.6.2.1. Cabozantinib

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

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, TIA and MI) and venous thrombotic AEs (eg, deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscesses, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; also known by the preferred term posterior reversible encephalopathy syndrome [PRES]).

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

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPE, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 8).

Cabozantinib should be permanently discontinued for the following AEs, regardless of whether these events are deemed related to cabozantinib: visceral perforation or fistula formation, serious and life-threatening rhabdomyolysis, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertension with life-threatening consequences, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

6.6.2.1.1. Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2012) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 11. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

Table 11: Management of Diarrhea Associated with Cabozantinib

Status	Management

Tolerable Grade 1-2
(duration < 48 h)
	• Continue with study treatment and consider dose reduction
	• Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day])
	• Dietary modifications (eg, small lactose-free meals, bananas and rice)
	• Intake of isotonic fluids (1-1.5 L/day)
	• Re-assess after 24 hours:
	  o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval
	  o Diarrhea not resolving: Continue/resume antidiarrheal treatment

Intolerable Grade 2,
Grade 2 > 48 h,
or ≥ Grade 3
	• Interrupt study treatment
	• Ask subject to attend clinic
	• Rule out infection (eg, stool sample for culture)
	  o Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h)
	• Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities
	• For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration
	• Re-assess after 24 h
	  o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose
	  o Diarrhea not resolving: Start and or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 7.3.1 for further details).

6.6.2.1.2. Non-Gastrointestinal Fistula

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

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

6.6.2.1.3. Hemorrhage

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

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

6.6.2.1.4. 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. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

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

6.6.2.1.5. Hypertension

Table 12 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertension with life threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) or when urgent intervention is indicated.

Table 12: Management of Hypertension[a] Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
> 150 mm Hg (systolic) [a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic and < 100 mm Hg diastolic. • If subject is symptomatic interrupt cabozantinib treatment and restart only if symptoms have resolved and BP is < 150 mm Hg systolic and < 90 mm Hg diastolic.
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion. Treatment should be 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 sustained diastolic BP > 110 mm Hg, or if subject is symptomatic. • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic and < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. • Re-start cabozantinib treatment at reduced dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 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.

BP, blood pressure; MI, myocardial infarction.

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

6.6.2.1.6. Stomatitis and Mucositis

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

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

6.6.2.1.7. Skin and Subcutaneous Tissue Disorders

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

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery and at least 5 days before an optional tumor biopsy. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing; subjects should be allowed to heal for at least 10 days after optional tumor biopsies.

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

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms

such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPE are summarized in Table 13.

Table 13: Management of Palmar-plantar Erythrodysesthesia Associated with Cabozantinib

CTCAE v5 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if 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 (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue subject from study treatment if PPE does not improve within 6 weeks.

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

6.6.2.1.8. Osteonecrosis

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

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

Advise subjects regarding oral hygiene practice and to quickly report symptoms to the Investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

6.6.2.1.9. Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 14 provides treatment guidelines for proteinuria deemed related to cabozantinib.

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

Table 14: Management of Proteinuria Associated with Cabozantinib

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

UPCR, urine protein/creatinine ratio.

6.6.2.1.10. Nervous System Disorders

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

RPLS (also known as PRES) 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.

6.6.2.1.11. Infections and Infestations

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

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

6.6.2.1.12. Blood and Lymphatic System Disorders

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

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

6.6.2.1.13. 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.

6.6.2.1.14. Weight Loss

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

6.6.2.1.15. Corrected QT Prolongation

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

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

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline per ECG evaluation at the site, 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 an increase of > 60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension) or those with 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
- Send copies of ECGs to central ECG laboratory for independent read
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms and the average increase is ≤ 60 ms above baseline or a consulting cardiologist or appropriate expert determines that the frequency of ECGs may revert to the schedule in the protocol.

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

- Symptoms are determined to be unrelated to the QT interval prolongation

- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms and ≤ 60 ms above baseline.
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

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

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

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

6.6.2.1.16. Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Table 8 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or IV replacement.

6.6.2.1.17. Endocrine Disorders

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

6.6.2.2. Atezolizumab

The most common AEs reported in ≥ 20% of subjects treated with atezolizumab include fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation (Tecentriq USPI).

Subjects treated with atezolizumab may also develop IRRs or CRS as well as irAEs such as myocarditis, pericardial disorders, pneumonitis, hepatitis, colitis, nephritis, endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, Type 1 diabetes), skin disorders, severe cutaneous adverse reactions, ocular events, neurological toxicity (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, meningoencephalitis, facial paresis, or myelitis), pancreatitis, myositis, and embryo-fetal toxicity. Management guidance for atezolizumab-associated AEs is provided in Sections 6.6.2.2.1 through 6.6.2.2.15.

For details on warnings & precautions, possible AEs and management guidance of AEs, and use in special patient populations refer to the local prescribing information of atezolizumab and the atezolizumab Investigator's Brochure. In addition, Investigators may be informed separately of any new urgent safety concerns that may arise through direct communication from the Sponsor (eg, Dear Investigator Letters).

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

- Subjects 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.
- 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 (1-2 mg/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 for a given subject prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to re-challenge subjects with atezolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.1. Infusion-Related Reactions and Cytokine Release Syndrome

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-1 or PD-L1 (Rotz et al 2017; Adashek and Feldman 2019), including atezolizumab.

No premedication is indicated for the first administration of atezolizumab. However, subjects who experience an IRR or CRS with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (eg, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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 medical management of IRRs and CRS are provided in Appendix G.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-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 investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

For subjects who develop COVID-19 while on study, the Investigator is to evaluate the overall risk-benefit ratio for the subject to determine whether holding study treatment(s) is in the best interest of the subject.

6.6.2.2.2. Immune-Related Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Subjects should be assessed for pulmonary signs and symptoms throughout the study and will also have 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 infections, 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 15.

Table 15: Management Guidelines for Immune-Related Pulmonary Events, Including Pneumonitis

Severity of Event	Management
Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider subject referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better. [b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding 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
Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone 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 period of time beyond 12 weeks to allow for corticosteroids 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 requirements for duration of treatment and documented by the Investigator a. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge subjects with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

6.6.2.2.3. Immune-Related Colitis or Diarrhea

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 16.

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 (eg, 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 16: Management Guidelines for Immune-Related Diarrhea or Colitis

Severity of Event	Management
Grade 1	• Continue atezolizumab • Initiate symptomatic treatment • Endoscopy is recommended if symptoms persist for > 7 days • Monitor closely
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Initiate symptomatic treatment • If strong clinical suspicion for immune-related colitis, start empiric IV steroids while waiting for definitive diagnosis • Subject 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 or equivalent. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Resume atezolizumab if event resolves to Grade 1 or better [a,b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab [c]
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer subject 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. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Resume atezolizumab if event resolves to Grade 1 or better [b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab [c]
Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor. [c] • Refer subject 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. • 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; IV, intravenous

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids 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 assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.4. Immune-related Endocrinopathies

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 17.

Monitor for signs and symptoms of hypophysitis. Subjects with unexplained symptoms such as headache, fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The subject should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone and free triiodothyronine and FT4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (eg, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 17: Management Guidelines for Endocrine Events

Event	Management
Hypophysitis (pan-hypopituitarism) Grade 2-3	• Withhold atezolizumab for up to 12 weeks after event onset [b] • Refer subject 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 therapy 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 and contact the Sponsor.[c] • For recurrent hypophysitis, treat as a Grade 4 event.

Event	Management
Hypophysitis (pan-hypopituitarism) Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject 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.[a] • Initiate hormone replacement therapy if clinically indicated.
Grade 1 hypothyroidism	• Continue atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH closely
Grade 2 hypothyroidism	• Consider withholding atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH closely • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving
Grade 3 and 4 hypothryoidism	• Withhold atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH closely • Refer to an endocrinologist • Admit patient 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 and contact the Sponsor for life threatening immune-related hypothyroidism[c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L**: • Continue atezolizumab • Monitor TSH every 4 weeks • Consider subject referral to endocrinologist **TSH < 0.1 mU/L**: • Follow guidelines for Grade 2 hyperthyroidism • Consider subject referral to endocrinologist
Grade 2 hyperthyroidism	• Consider withholding atezolizumab • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider subject referral to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed • Refer to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Permanently discontinue atezolizumab and contact the Sponsor for life threatening immune-related hyperthyroidism[c]
Symptomatic adrenal insufficiency Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer subject 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. • Resume atezolizumab if event resolves to Grade 1 or better and subject is stable on replacement therapy[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better or subject is not stable on replacement therapy while withholding atezolizumab[c]
Hyperglycemia Grade 1 or 2	• Continue atezolizumab • Investigate for diabetes. If subject has Type 1 diabetes, treat as Grade 3 event. If subject 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. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

IV, intravenous; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.5. Immune-Related Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, 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 18.

Table 18: Atezolizumab Management Guidance of Immune-Related Dermatologic Events

Severity of Event	Management of Skin Disorder
Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines).
Grade 2	• Continue atezolizumab. • Consider subject 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 • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Grade 3	• Delay atezolizumab for up to 12 weeks after event onset [a] • Refer subject 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. • Resume atezolizumab if event resolves to Grade 1 or better.[b] • Permanently discontinue atezolizumab and contact Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab.[c]
Grade 4	• Permanently discontinue atezolizumab and contact Sponsor.[c]

Severity of Event	Management of Skin Disorder
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 subject 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 period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements 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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.6. Immune-Related Ocular Events

Treatment-emergent ocular events have been associated with atezolizumab. An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events). Management guidelines for ocular events are provided in Table 19.

Table 19: Atezolizumab Management Guidance of Immune-Related Ocular Events

Severity of Event	Management of Ocular Event
Grade 1	• Continue atezolizumab. • Subject 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.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Subject referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • Resume atezolizumab if event resolves to Grade 1 or better.[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab.[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject 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 period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements 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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab shoud be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.7. Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, or 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 subjects 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.

Subjects with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 20.

Table 20: Management Guidelines for Immune-Related Meningoencephalitis

Severity of Event	Management
All grades	• Permanently discontinue atezolizumab and contact the Sponsor [a] • Refer subject 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

IV, intravenous.

[a] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.8. Immune-Related Motor and Sensory Neuropathy

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 21, with specific guidelines for myelitis provided in Table 22.

Table 21: Management Guidelines for Immune-Related 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 subject to neurologist • Initiate treatment as per institutional guidelines • For general immune-related neuropathy: - Resume atezolizumab if event resolves to Grade 1 or better[b] - Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab [c] • For facial paresis: - If event resolves fully, resume atezolizumab [b] - If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor. [c]
Immune-related neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor [c] • Refer subject to neurologist • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome, any grade	• Permanently discontinue atezolizumab and contact the Sponsor [c] • Refer subject to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

IV, intravenous.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 22: 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 and contact the Sponsor. • 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 and contact the Sponsor. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

6.6.2.2.9. Immune-Related Pancreatitis

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up 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 23.

Table 23: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 1	• Continue atezolizumab • Monitor amylase and lipase prior to dosing
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 (eg, > 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 event
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject 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 • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab [c]

Event	Management
	• For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c]
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer subject 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 • Resume atezolizumab if event resolves to Grade 1 or better [b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab [c] • For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor [c] • Refer subject 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; IV, intravenous; ULN, upper limit of normal.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.10. Immune-Related Nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study 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.

Atezolizumab should be withheld for moderate (Grade 2) immune-related nephritis and permanently discontinued for severe nephritis (Grade 3 or 4). Refer subjects to a renal specialist and consider renal biopsy and supportive measures as indicated. Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated. Refer to the current atezolizumab Investigator's Brochure for further guidance on the management of immune-related nephritis.

Subjects with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 24.

Table 24: Management Guidelines for Immune-Related Nephritis

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, 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 and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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 (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the Investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.11. Immune-Related Cardiac Events

Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any subject presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (eg, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, eg, in a subject 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 25.

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 (see section on myocarditis above).

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 25. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 25: Management Guidelines for Immune-Related Cardiac Events

Event	Management
Immune-related myocarditis, Grades 2-4 Immune-related pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab and contact the Sponsor.[a] • Refer subject to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD 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.

[a] ECMO, extracorporeal membrane oxygenation; IV, intravenous; VAD, ventricular assist device.

Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by the investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.12. Immune-Related Myositis

Myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-kinase increase), and imaging (electromyography/MRI) features and is confirmed with a muscle biopsy.

Subjects with possible myositis should be referred to a rheumatologist or neurologist. Subjects with possible myositis should be monitored for signs of myocarditis.

Subjects with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines presented in Table 26.

Table 26: Management Guidelines for Immune-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines

Event	Management
Immune-related myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Sponsor. • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroid 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,
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact the Sponsor • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, 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, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor. Permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Sponsor.
Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, 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.

Event	Management

IV, intravenous

[a] Atezolizumab may be withheld for a period of time (ie, > 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 an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge subjects with atezolizumab should be based on Investigator's assessment of benefit-risk, and documented by the Investigator. The Medical Monitor is available to advise as needed.

6.6.2.2.13. 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.

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

- Fever ≥ 38.5°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 < 100×10^9/L (100,000/μL)
  - ANC < 1.0×10^9/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 interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Subjects with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al (2016). A febrile subject 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 ≤ 181 × 10^9/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Subjects with suspected HLH or MAS should be treated according to the guidelines in Table 27.

Table 27: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosisor Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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, contact Sponsor and 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. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

HLH, hemophagocytic lymphohistiocytosis; IV, intravenous; MAS, macrophage activation syndrome

6.6.2.2.14. Other Atezolizumab-Associated Immune-Related Adverse Events

The following general management guidance should be applied for any other atezolizumab-associated irAEs:

- Grade 2 or 3: delay atezolizumab dosing up to 12 weeks until irAE recovers to Grade 0-1 and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
- Grade 4 or recurrent Grade 3: permanently discontinue atezolizumab

6.6.2.2.15. Embryo-Fetal Toxicity

Based on its mechanism of action, atezolizumab can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. If atezolizumab is used during pregnancy, or if the subject becomes pregnant while taking atezolizumab, advise the subject of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with atezolizumab and for at least 5 months after the last dose.

6.6.2.3. Sorafenib

The most common adverse reactions (≥ 20%) for sorafenib are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, GI and abdominal pains, hypertension, and hemorrhage.

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

Temporary interruption of sorafenib is recommended in subjects undergoing major surgical procedures. Temporary interruption or permanent discontinuation of sorafenib may be required for the following:

- Cardiac ischemia or infarction
- Hemorrhage requiring medical intervention
- Severe or persistent hypertension despite adequate anti-hypertensive therapy
- GI perforation
- QTc prolongation
    - If at any time on study there is an increase in QTcF to an absolute value > 500 ms or > 60 ms above the baseline value, 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 > 60 ms above baseline, the following actions must be taken:
        - Discontinue treatment
        - Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension) or those with a significant ventricular arrhythmia on ECG for a thorough cardiology evaluation and management

- Send copies of ECGs to central ECG laboratory for independent read

- Severe DILI

For additional details on warnings, precautions, possible AEs and management guidance of AEs refer to the most current local prescribing information appropriate to the respective study site location.

6.6.2.4. Management of Hepatobiliary Adverse Events

As this study will be evaluating subjects with advanced HCC, hepatobiliary AEs are expected to occur relatively frequently.

Elevations of aminotransferases and bilirubin have been observed during treatment with some anticancer therapies including cabozantinib, atezolizumab, and sorafenib. Modifications of study treatment may be appropriate to address these events, and management guidance for these agents in response to increases in aminotransferases and bilirubin is provided in this section.

General Guidance for Aminotransferase and Bilirubin Abnormalities

Patients with advanced liver cancer may have elevations of aminotransferases (ALT and AST) or bilirubin due to their disease. As such, subjects on this study may enroll with elevations of AST/ALT up to 5 × ULN at baseline. It is recommended that subjects with elevations of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters.

Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Subjects 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.

Guidance for Management of Hepatotoxicity

Guidance is provided on management of hepatotoxicity related to atezolizumab in Table 28 and to cabozantinib in Table 29.

Table 28: Management Guidelines for Hepatic Events Associated with Atezolizumab

Severity of Event	Management
If AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN **or** If AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN **or** If AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	**All events:** • Monitor LFTs more frequently until return to baseline values. • Withhold atezolizumab for up to 12 weeks after event onset.[a] • For events of > 5 days' duration, consider initiating treatment with 1-2 mg/kg/day prednisone or equivalent. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor.[c]
If AST or ALT increases to > 10 × ULN **or** total bilirubin increases to > 3 × ULN	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Consider subject referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1-2 mg/kg/day prednisone or equivalent. • If event does not improve within 48 h after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; LFT, liver function test; ULN, upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (ie, > 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 requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 subjects who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge subjects with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 29: Management Guidelines for Hepatic Events Associated with Cabozantinib

Severity of Event	Management
If ALT/AST is ≤ 3.0 × ULN at baseline and increases to ≥ 5.0 × ULN	• Interrupt cabozantinib • Monitor LFTs more frequently until return to baseline values • If event resolves to baseline, or values stabilize at clinically acceptable levels, cabozantinib may be resumed at a reduced dose • Discontinue cabozantinib if hepatic dysfunction is not reversible despite temporary interruption of cabozantinib or drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with DILI
If ALT/AST is > 3.0 × ULN to ≤ 5.0 × ULN at baseline and doubles compared with the baseline values **OR** If ALT/AST is > 3.0 × ULN to ≤ 5.0 × ULN at baseline and increases are less than double but are accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests (eg, INR).	• Interrupt cabozantinib • Monitor LFTs more frequently until return to baseline values. • If event resolves to baseline, or values stabilize at clinically acceptable levels, cabozantinib may be resumed at a reduced dose • Discontinue cabozantinib if hepatic dysfunction is not reversible despite temporary interruption of cabozantinib or drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with DILI

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; INR, international normalized ratio; LFT, liver function test; ULN, upper limit of normal.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency. Hepatic encephalopathy is not uncommon in HCC patients and can be due to acute liver failure, portal systemic shunting and cirrhosis (Wong et al 2011, Willson et al 2013).

The clinical manifestations of HE include a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma (Vilstrup et al 2014). As HE progresses, personality changes, such as apathy, irritability, and dis-inhibition may be observed. In the most severe form of HE, affected individuals may develop marked confusion or disorientation, amnesia, greatly dulled or reduced consciousness (stupor), or loss of consciousness (coma).

In the Sponsor-conducted CELESTIAL XL184-309 study, there was a higher incidence of hepatic encephalopathy and encephalopathy in the cabozantinib arm as compared to the placebo arm, and the median time to onset in the cabozantinib arm was 5.9 weeks. Cabozantinib has been associated with diarrhoea, vomiting, decreased appetite, and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Additionally, a higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Furthermore, no cases of hepatic encephalopathy were reported in the RCC studies (METEOR and CABOSUN).

There is no specific test used to diagnose HE. The diagnosis of HE is usually based on a combination of medical history, symptoms, and a clinical exam. Blood tests (eg, ammonia levels) can identify abnormalities associated with liver, kidney, and other conditions that may contribute to HE. High blood-ammonia levels alone are not confirmatory or prognostic. However, if a subject's ammonia is normal, HE is less likely.

Patients with liver insufficiency and altered mental status should be evaluated for alternative causes of brain dysfunction, including irAEs. Rare cases (0.4% of patients) of meningoencephalitis have been observed in patients who received atezolizumab monotherapy (see the atezolizumab IB for more information). Additionally, the existence of precipitating factors for HE (diarrhea, vomiting, decreased appetite, infections, electrolyte abnormalities, gastrointestinal [GI] bleeding, diuretic overdose, and constipation) may aid in the diagnosis (Vilstrup et al 2014).

Adverse events of encephalopathy as graded per CTCAE v5.0 are shown below:

- Grade 1: Mild symptoms
- Grade 2: Moderate symptoms; limiting instrumental activities of daily living
- Grade 3: Severe symptoms; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

Management of Hepatic Encephalopathy

In patients with HE, the first step in management is to identify and treat the precipitating factors for HE including, but not limited to, diarrhea, vomiting, decreased appetite, electrolyte abnormalities, infections, GI bleeding, diuretic overdose, and constipation.

The following treatments are recommended (Vilstrup et al 2014):

- For symptomatic patients, consider treating with lactulose.
- After the initial episode, lactulose is recommended for prevention of recurrent episodes of HE.
- After the second episode, rifaximin is recommended as an add-on to lactulose for prevention of recurrent episodes of HE.
- Intravenous (IV) L-ornithine L-aspartate (LOLA) and branched-chain amino acids (BCAAs) can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy.
- Neomycin and metronidazole are alternative choices for treatment.

For patients with higher grades (≥ Grade 3) HE, consider hospitalization. Patients who are at risk or unable to protect their airway need more intensive monitoring and are ideally managed in an intensive care setting. Please refer to Vilstrup et al 2014 for further information. Detailed guidelines for the management of HE are provided in Table 30.

Table 30: Management of Hepatic Encephalopathy Associated with Study Treatment

Hepatic Encephalopathy CTCAE v5.0 Grade	**Recommended Guidelines for Management and Dose Modification**
Grade 1	Identify and treat any precipitating factor. If symptomatic, consider treatment for AEs. Continue study treatment if asymptomatic and an AE is manageable and tolerable.
Grade 2	Consider treatment for AEs. Continue study treatment if an AE is manageable and tolerable or interrupt study treatment for grade 2 AEs that are intolerable or cannot be adequately managed. If an irAE is suspected, consider initiating steroid treatment.
Grade 3	Consider hospitalization. If an irAE is suspected, consider initiating steroid treatment. Interrupt study treatment; Sponsor must be contacted to discuss treatment continuation upon resolution of AEs. Study treatment may resume if the toxicity can be easily managed with a dose reduction and optimal medical care.
Grade 4	Discontinue study treatment. Consider hospitalization. If an irAE is suspected, consider initiating steroid treatment.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; HE, hepatic encephalopathy; irAE, immune-related adverse event.

Hepatic Failure

Hepatic failure is a disorder characterized by liver dysfunction. Hepatic failure can be severe and life-threatening. Hepatic failure may develop rapidly over days or weeks (acute) or gradually over months or years (chronic). Hepatic failure can also develop in the setting of HCC when the functional reserve of the hepatocytes has declined. Clinical findings potentially indicating hepatic failure include, but are not limited to: jaundice, portal hypertension, ascites, HE, GI bleeding, and kidney failure. Laboratory findings include abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (ie, International Normalized Ratio [INR]).

Acute hepatic failure should be treated urgently as symptoms can worsen quickly. Subjects with acute hepatic failure may need to be treated in an intensive care setting.

Adverse events of hepatic failure are graded per CTCAE v5.0 as below:

- Grade 3: Asterixis; mild encephalopathy; DILI; limiting self-care (activities of daily living)
- Grade 4: Life-threatening consequences; moderate to severe encephalopathy; coma
- Grade 5: Death

For management of hepatic failure related encephalopathy and aminotransferase and bilirubin abnormalities (including DILI), refer to the guidance described above in this section. For Grade 4 events of hepatic failure, discontinue study treatment and treat symptoms accordingly.

7. CONCOMITANT MEDICATIONS AND THERAPIES

7.1. Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).

- Bisphosphonates can be used per standard of care if the benefit outweighs the risk per the Investigator's discretion (Section 6.6.2.1.8).

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates. 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.

- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.

- Inhaled, intranasal, intra-articular, or topical corticosteroids are allowed if minimal systemic absorption. Systemic corticosteroids are allowed for control of infusion reactions or irAEs and must be tapered over ≥ 1 month to a dose level ≤ 10 mg/day of prednisone equivalent before next atezolizumab administration. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed, and short term treatment with systemic corticosteroids for acute medical conditions (eg, exacerbation of chronic obstructive pulmonary disease [COPD]) is allowed if clinically indicated.

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

  - *Low dose LMWH for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.

  - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of DVT), and the benefit outweighs the risk per the

investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.6.2.1.4.

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

- For restrictions on oral anticoagulants see Section 7.2.

- Considerations for use of COVID-19 vaccine: At this time, there are limited data available for the use of COVID-19 vaccines in specific subsets of individuals such as the immunocompromised and cancer patients, including those receiving anticancer therapies such as cabozantinib, atezolizumab, and sorafenib. The decision to proceed with vaccination for subjects enrolled in this clinical study rests with the treating physician and the subject and should be taken after consideration of all safety precautions provided by the manufacturers of the vaccines and local health authorities. Please note, immunizations with live, attenuated COVID-19 vaccines or any experimental vaccines are not allowed. Exelixis will monitor all available information and provide additional guidance as appropriate.

Potential drug interactions with cabozantinib, atezolizumab, and sorafenib are summarized in Section 7.3.1, Section 7.3.2, and Section 7.3.3, respectively.

7.2. Prohibited or Restricted Therapy

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

- Any investigational agent or investigational medical device.

- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).

- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

- Concomitant use of denosumab with atezolizumab is prohibited due to a potential for increased risk of infections.

- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 7.1.

- Metamizole (dipyrone) because of its potential for causing agranulocytosis.

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

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established. If clinically unavoidable the investigator should consult the Sponsor prior to the procedure for safety guidance.

- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects until they have permanently discontinued cabozantinib or sorafenib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

- Live vaccines are prohibited while on study and until 5 months after last atezolizumab dose (eg, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin, yellow fever, varicella, and TY21a typhoid vaccines). The use of inactivated (killed) vaccines for the prevention of infectious disease requires Sponsor approval with the exception of an inactivated influenza vaccine, which can be given without Sponsor approval.

- Chronic co-administration of cabozantinib or sorafenib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease concentrations of these study drugs 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 or sorafenib, as this could significantly increase the exposure to these study drugs.

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase concentrations of study drug and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of these study drugs and should be avoided.

Additional information on potential drug interactions with cabozantinib, atezolizumab, and sorafenib are summarized in Section 7.3.1, Section 7.3.2, and Section 7.3.3, respectively.

7.3. Potential Drug Interactions

7.3.1. Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration-vs-time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce CYP enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (ie, AUC) to cabozantinib.

Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

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

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

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein (eg, fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). In addition, cabozantinib was shown to be a substrate of drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay. Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (eg, cyclosporine, efavirenz, emtricitabine) should be approached with caution. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

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

7.3.2. Potential Drug Interactions with Atezolizumab

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted. There are no known interactions with other medicinal products or other form of interactions. For additional details refer to the local prescribing information and the atezolizumab Investigator's Brochure.

7.3.3. Potential Drug Interactions with Sorafenib

Concomitant use of strong CYP3A4 inducers (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort), should be avoided when possible, because these drugs can decrease the systemic exposure to sorafenib. Bleeding and INR elevations have been reported in patients receiving both warfarin and sorafenib; subjects in the sorafenib comparator arm taking concomitant warfarin should be monitored for changes in PT and INR and for clinical bleeding episodes. For additional details refer to the local prescribing information appropriate to the local site location.

8. SAFETY

8.1. Adverse Events and Laboratory Abnormalities

8.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study 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 an investigational product, regardless of whether or not the event is assessed as related to the investigational product. This requirement includes specific events or symptoms associated with cancer progression or general clinical deterioration to ensure potential toxicities are not overlooked. Radiographic progression without associated clinical sequelae is not considered an AE; terms such as 'disease progression' should be avoided. Pre-existing medical conditions that worsen during a study will be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 8.1.2.

All untoward events that occur after informed consent through 30 days (100 days for SAEs and AESIs) after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to discontinue all study treatment or the date of the last dose of any study treatment) are to be recorded in the source documents by the investigational site.

At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report.

Assessment of the relationship of the AEs to study treatment by the investigator will be based on the following two definitions:

- **Not Related**: An event is assessed as not related to study treatment if it is attributable to another cause and/or there is no evidence to support a causal relationship.
- **Related**: An event is assessed as related to study treatment when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study treatment and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

8.1.2. Laboratory Abnormalities

All laboratory data required by this protocol and any other clinical investigations will be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the Investigator will be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

8.2. Serious Adverse Events

8.2.1. Definitions

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

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

- Results in death.
- Is immediately life-threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
- Results in significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

As soon as an investigator becomes aware of an AE that meets the criteria for an SAE, the investigator will document the SAE to the extent that information is available.

SAEs, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the investigator's knowledge of the event by submitting the completed SAE report

form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites.

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

- All SAEs that occur after informed consent and through 100 days after the date of the decision to permanently discontinue study treatment (ie, the later of the date of the decision of the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject) or the date the subject is deemed to be a screen failure.

- Any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 100 days after the date of the decision to permanently discontinue study treatment.

Note: If the subject does not meet the eligibility criteria during screening, then SAEs only need to be reported from the time the subject signs the informed consent until the day when the subject has been determined to not be eligible for study participation.

SAEs that occur after consent through 100 days after the date of the decision to permanently discontinue of study treatment must also be recorded on the CRF page.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, and an event description. Other important information requiring timely reporting are the SAE term(s), the reason why the event is considered to be serious (ie, the seriousness criteria), and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event will be recorded on the SAE form.

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 the Sponsor's Drug Safety personnel or designee.

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.

- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:

    - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

    - Prespecified study hospitalizations for observation.

    - Events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

8.2.2. Regulatory Reporting

The Sponsor's Drug Safety group (or designee) will process and evaluate all SAEs and AESIs as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor's Drug Safety group (or designee) will assess the expectedness of each SAE to the study treatment using the current reference safety information (RSI) for each study drug.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with FDA regulations (21 Code of Federal Regulations [CFR] 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the Investigator to his or her IRB/ECs will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

8.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) consist of immune-mediated AEs associated with ICIs, cases of potential DILI, and suspected transmission of an infectious agent by the study treatment (Table 31).

AESIs will be reported to the Sponsor or designee using the SAE reporting form irrespective of whether the event is serious or nonserious; all AESIs must be reported within 24 hours using the SAE process as described in Section 8.2.

Guidance for management of immune-mediated AEs associated is provided in Section 6.6.2.2 and can also be found in the local prescribing information and Investigator's Brochure for atezolizumab.

Table 31: Adverse Events of Special Interest

Category	Event
DILI	• Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin) o Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice
Other	• Suspected transmission of an infectious agent by the study treatment, as defined below
	o Any organism, virus, or infectious particle (eg, 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 study treatment is suspected.
irAE	• Pneumonitis
irAE	• Colitis
irAE	• Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
irAE	• Hepatitis, including AST or ALT > 10 × ULN
irAE	• Systemic lupus erythematosus
irAE	• Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myelitis, and facial paresis
irAE	• Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
irAE	• Nephritis
irAE	• Ocular toxicities (eg, uveitis, retinitis)
irAE	• Myositis
irAE	• Myopathies, including rhabdomyolysis
irAE	• ≥ Grade 2 cardiac disorders
irAE	• Vasculitis
irAE	• Severe cutaneous reactions (eg, Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; irAE, immune-related adverse event; ULN, upper limit of normal.

8.3.1. General Information on Immune-Related Adverse Events

The immune-modulating properties of checkpoint-inhibitors, such as the anti-PD-L1 antibody atezolizumab, are able to unbalance immunologic tolerance and generate a subset of AEs (called irAEs) with an autoimmune inflammatory pathomechanism. Immune-related adverse events may involve any organ or tissue (Michot et al 2016). Most irAEs occur within the first 12 weeks of exposure to ICIs but some of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs are fatigue, fever, and chills. Organ-specific irAEs consist of dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively unspecific symptoms. Additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), FT4 and TSH (pituitary-thyroid function), luteinizing hormone (LH) and FSH (pituitary-gonadal function), adrenocorticotropic hormone (ACTH) and cortisol (pituitary-adrenal function).

Additional organ-specific irAEs include hepatitis (AST/ALT increases, hepatomegaly, periportal edema, periportal lymphadenopathy, lymphocyte infiltrates periportal and surrounding primary biliary ducts) and pneumonitis (acute interstitial pneumonia). Less frequent irAEs include neurologic disorders (myasthenia gravis, Guillain-Barré syndrome, aseptic meningitis, myelitis, facial paresis), ocular AEs (uveitis), renal AEs (interstitial nephritis), cardiac AEs (myocarditis), muscular AEs (myositis), skin-related AEs (Stevens-Johnson syndrome, toxic epidermal necrolysis), and pancreatic AEs (lipase increase).

8.4. Follow-Up of Adverse Events

Non-serious AEs (see below for AESIs [Table 31]) are to be recorded in the CRF until 30 days after the date of the decision to discontinue study treatment (the later of the date of the decision

by the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject). The status of unrelated SAEs that are ongoing after the date of the decision to discontinue study treatment will be documented as of the 100-day FU-2 visit.

All AESIs (regardless of seriousness) and all related SAEs that are ongoing 100 days after the date of the decision to discontinue study treatment (the later of the date of the decision by the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject), and AEs assessed as related that led to study treatment discontinuation that are ongoing 100 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to Grade 2 or lower
- The Investigator determines that the event has become stable or irreversible.

Further details on follow-up procedures are summarized in Appendix K.

8.5. Other Safety Considerations

8.5.1. Pregnancy

Use of highly effective methods of contraception is very important during the study and for 5 months after the last dose of study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have follow up for at least 6 months after birth. Furthermore, male subjects must refrain from donating sperm and are required to use condoms in order to avoid transmission of study treatment in semen for the duration of study treatment and through 5 months after their last dose of study treatment. If a female partner of a male subject becomes pregnant during the study, the Sponsor will ask the pregnant female partner to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth. Both male and female subjects should seek advice and consider fertility preservation before receiving study treatment.

The Investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies 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 the Sponsor or designee. 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 the following periods after discontinuing study treatment:

- **Cabozantinib + atezolizumab**: at least 5 months from the last dose of atezolizumab or 4 months from the last dose of cabozantinib, whichever is later
- **Sorafenib**: at least 2 weeks after the last dose of sorafenib
- **Single-agent cabozantinib**: at least 4 months from the last dose of cabozantinib

8.5.2. Medication Errors/Overdose

Medication error is defined as the administration of study drug medication outside or above the established dosing regimens per the specific protocol.

Any study medication overdose, misuse, abuse, or study medication error (excluding missed doses) that results in an AE or SAE requires reporting to the Sponsor or designee according to the guidance for AE and SAE reporting (Sections 8.1 and 8.2, respectively).

In case of overdose, the Sponsor medical monitor or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

Please refer to the Investigator's Brochure for additional management recommendations for an overdose of cabozantinib.

9. STATISTICAL CONSIDERATIONS

Details of the planned analyses, including sensitivity analyses or other strategies if needed to assess and address consequences of the COVID-19 pandemic on trial conduct and study data, will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before the last subject is randomized. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

9.1. Analysis Populations

The planned analysis populations to be employed for statistical analyses of data collected from subjects randomized during the global enrollment phase are briefly summarized in Table 32. These populations will include subjects in China randomized during the global enrollment phase. Subjects randomized during the Mainland China Extension Phase are excluded from these analyses; they will be included in separate analyses (see Section 9.9). Further information on these populations is provided in the sections below.

Table 32: Analysis Populations for the Global Enrollment Phase

Analysis	Population	Subjects
Primary PFS	PITT	First 372 subjects randomized to experimental or control arm (may be expanded to include the first 410 randomized subjects)
Primary OS	ITT	ITT subjects randomized to experimental or control arm
Secondary PFS	ITT	ITT subjects in control and single-agent cabozantinib arm
Additional efficacy analyses	ITT	All randomized subjects
Safety analyses	Safety	All subjects who received any study treatment

ITT, Intent-to-Treat; OS, overall survival; PFS, progression-free survival; PITT, PFS Intent-to-Treat.

9.1.1. Intention-to-Treat Population

The ITT population will consist of all subjects who are randomized to any of the three study treatment arms (the experimental arm [cabozantinib plus atezolizumab], the single-agent

cabozantinib arm, or the control arm [sorafenib]) during the global enrollment phase, regardless of whether any study treatment or the correct study treatment is received. This population will be used for the primary OS analysis to compare the combination arm with the control arm (sorafenib), and also for the secondary PFS analysis to compare the single-agent cabozantinib arm with the control arm (sorafenib). Subjects randomized during the Mainland China Extension Phase are excluded from this population; they will be included in separate analyses (see Section 9.9).

9.1.1.1. PFS Intention-to-Treat Population

The first 372 subjects that are randomized (based upon Greenwich Mean Time randomization date/time values) to the experimental (cabozantinib and atezolizumab, n=248) arm and control (sorafenib, n=124) arm will be considered as the PFS Intent-to Treat (PITT) population. The population may be extended to the first 410 subjects randomized to the two groups if a review of accumulating events suggests that the number of events required will not be reached (due to censoring) among the first 372 subjects originally planned. This population will be used for the primary PFS analysis to compare these arms.

9.1.2. Safety Population

The Safety population will consist of all subjects who randomized during the global enrollment phase and receive any amount of study treatment. Analyses based on Safety population will be performed according to the actual treatment received for the length of the study. Data handling rules for subjects in the experimental/control arm who received incorrect study treatment will be described in the SAP. Subjects randomized during the Mainland China Extension Phase are excluded from this population; they will be included in separate analyses (see Section 9.9).

9.2. Primary Efficacy Endpoints

The two primary efficacy endpoints are duration of PFS and OS. Subjects randomized to the experimental (cabozantinib and atezolizumab) arm and control (sorafenib) arm during the global enrollment phase will be considered for these analyses. Subjects randomized during the Mainland China Extension Phase will not be included in these analyses; they will be included in separate analyses (see Section 9.9).

9.2.1. Definitions

9.2.1.1. Duration of Progression-Free Survival

Duration of PFS is defined as the time from randomization to the earlier of either radiographic PD per RECIST 1.1 or death due to any cause. The definition of disease progression and censoring rules for the primary analysis are described in Section 9.2.2.

9.2.1.2. Duration of Overall Survival

Duration of OS is defined as the time from date of randomization to date of death due to any cause. For subjects who are alive at the time of data cutoff or are permanently lost to follow-up, duration of OS will be right censored at the earlier of the following: date the subject withdrew consent from all follow-up, data cutoff date, or the date the subject was last known to be alive.

9.2.2. Primary Analysis

9.2.2.1. Progression-Free Survival

The primary analysis of PFS is event-driven and will be conducted after at least 257 events have been observed in the PITT population (see Section 9.1.1.1). It is designed to include progression events as determined by the BIRC per RECIST 1.1. Clinical deterioration determined by the investigator will not be considered progression events.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive systemic NPACT or nonprotocol radiation therapy (other than to bone) or surgery to resect target lesions before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of subsequent therapy/surgery. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment post randomization that is on or prior to the data cutoff. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

- Subjects who miss 2 or more scheduled tumor assessments followed by an event will be right censored on the date of their most-recent tumor assessment prior to the missing assessments. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided 0.01 level of significance. The stratification factors will be the same as those used to stratify the randomization (see Section 3.3).

The median duration of PFS and the associated 95% and 99% CIs for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% and 99% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

In the primary analysis of PFS, if the p-value for the stratified log-rank test is statistically significant and the HR ($\lambda_{\text{cabozantinib + atezolizumab}}/\lambda_{\text{sorafenib}}$) is < 1, the null hypothesis of no difference between the two treatment arms in PFS will be rejected and it will be inferred that PFS is superior in the group receiving cabozantinib + atezolizumab compared with the group receiving sorafenib.

9.2.2.2. Overall Survival

The primary analysis of OS is event-driven and will be conducted after at least 368 deaths have been observed in the ITT population (Section 9.1.1) for the experimental and control arms.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided α level of significance (the α level will be defined per Section 9.5). The stratification factors will be the same as those used to stratify the randomization.

The median duration of OS and the associated 95% and 1-α % CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% and 1-α % CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

Details of interim analyses of OS are provided in Section 9.8.

At any analysis of OS (interim or primary), if the p-value for the stratified log-rank test is statistically significant and the HR ($\lambda_{\text{cabozantinib + atezolizumab}}/\lambda_{\text{sorafenib}}$) is < 1, the null hypothesis of no difference in OS between the two treatment arms will be rejected and it will be inferred that OS is superior in the group receiving cabozantinib + atezolizumab compared with the group receiving sorafenib.

9.2.2.3. Supportive Analyses

Supportive (sensitivity) analyses will be conducted using all PFS events and subjects in the ITT population (Section 9.1.1) for the experimental and control arms at the time of the primary PFS analysis in the PITT population (see Section 9.1.1.1). Additional sensitivity analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing assessments, address bias due to tumor assessment timing, and to evaluate the impact of potentially informative censoring. These analyses will be performed using the same statistical methods described for the primary analysis.

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables on PFS and OS will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.3. Secondary Efficacy Endpoint

Formal hypothesis testing is planned for the secondary efficacy endpoint of PFS per BIRC for the single-agent cabozantinib arm vs the control arm (sorafenib).

9.3.1. Progression Free Survival (PFS) per BIRC between Single-Agent Cabozantinib and Control Arms

The analysis of PFS as a secondary endpoint is event-driven and will be conducted after at least 283 events have been observed in the ITT population (see Section 9.1.1) for the single-agent cabozantinib and control arms. It is designed to include progression events as determined by the BIRC per RECIST 1.1. General censoring rules as described in Section 9.2.2.1 will be applied.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test at the 2-sided α level (the α level will be defined per Section 9.5) in the ITT population, provided the null hypothesis for either PFS or OS is rejected in favor of the experimental arm (cabozantinib + atezolizumab) as described in Section 9.5. The stratification factors will be the same as those used to stratify the randomization (see Section 3.3).

The median duration of PFS and the associated 95% and 99% CIs for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% and 99% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

In the secondary analysis of PFS, if the p-value for the stratified log-rank test is statistically significant and the HR ($\lambda_{\text{cabozantinib}} / \lambda_{\text{sorafenib}}$) is < 1, the null hypothesis of no difference between the two treatment arms in PFS will be rejected and it will be inferred that PFS is superior in the group receiving single-agent cabozantinib compared with the group receiving sorafenib.

One interim analysis of secondary PFS is planned at approximately 67% information fraction. Details are provided in Section 9.8.

9.4. Additional Endpoints

Details of the planned analyses of these endpoints will be provided in the SAP:

- ORR, TTP, and DOR per RECIST 1.1 by BIRC and Investigator
- Evaluation of radiographic response per modified RECIST (mRECIST)
- Safety through the evaluation of AEs, including irAEs and other AESIs
- Characterization of the PK of cabozantinib in subjects with previously untreated HCC
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Change in serum AFP from baseline

- Correlation of biomarker analyses with clinical outcomes
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)
- Healthcare resource utilization

9.5. Control of Type I Error

Inflation of Type 1 error associated with testing of multiple primary endpoints and a secondary efficacy endpoint (PFS between single-agent cabozantinib and control) will be controlled by a modified Bonferroni procedure, a gatekeeping technique, and the fallback method (FDA 2017). Initially, the study-wise 2-sided alpha of 5% will be unequally allocated between primary endpoints PFS (1%) and OS (4%). The secondary PFS endpoint will be tested at the 1% level only if the primary PFS test is successful. If the null hypotheses are rejected for both the primary and secondary PFS endpoints, the 1% alpha for PFS will be reallocated to OS, allowing it to be tested at the 5% level.

Two interim analyses of OS are planned at the 33% and 66% information fractions (the first interim will coincide with the primary analysis of PFS and will be performed only if the null hypothesis for PFS is rejected and is expected to occur at approximately the 33% information fraction). One interim analysis is planned for secondary PFS endpoint contemporaneous with the primary PFS analysis with anticipated information fraction of 67%. Type 1 error associated with interim analyses will be controlled using Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending functions based upon a 4% total alpha allocation for OS and 1% for secondary PFS.

The testing and alpha reallocation are elucidated below.

First, test primary PFS at the 1% level. Then:

1. If primary PFS is significant:
    a. Re-allocate its 1% alpha to secondary PFS per the fallback method.
    b. Conduct interim analysis of OS at 33% per LD-OF with 4% total alpha
    c. Conduct interim analysis of secondary PFS endpoint at 67% per LD-OF with 1% alpha.
        i. If interim analysis of secondary PFS is significant:
            - Re-allocate its 1% alpha to OS
            - Conduct interim analysis of OS at 66% per LD-OF with 5% alpha
            - No further inferential testing of secondary PFS will be performed.

ii. If interim analysis of secondary PFS is not significant:
    - The final analysis of secondary PFS will be conducted at an alpha of 0.0096.
    - The alpha of subsequent OS analyses will be dependent on the timing and result of the final secondary PFS analysis.
        - The second interim analysis and the final for OS will be conducted per LD-OF with 4% alpha, if the second interim analysis occurs prior to the final analysis for secondary PFS, or, if it occurs after the final secondary PFS analysis where the final secondary PFS fails to reject its null hypothesis.
        - The subsequent OS analyses will be conducted per LD-OF with 4.96% alpha if it occurs after the rejection of the null hypothesis for secondary PFS.

d. Conduct interim and final analyses of OS with appropriate alpha as determined above

2. If primary PFS is not significant:
    a. Secondary PFS analysis cannot be conducted
    b. Conduct interim and final analyses of OS per LD-OF with 4% total alpha
        i. If OS is not significant at final analysis, procedure ends

All other statistical evaluations of efficacy will be considered exploratory.

9.6. Safety Analyses

All safety analyses will be performed using the Safety population (see Section 9.1.2). No formal statistical comparisons between these two treatment arms are planned.

9.6.1. Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The Investigator will classify the severity of AEs using CTCAE v5 and will judge each event to be “not related” or “related” to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after the date of first dose of study treatment. Only TEAEs with an onset date prior to date of decision for treatment discontinuation (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment) + 30 days (+ 100 days for SAEs and certain other AEs; Section 8.3) will be tabulated in summary tables.

The frequency and percentage of subjects with TEAEs will be tabulated for overall incidence by system organ class and/or preferred term by treatment arm. Related TEAEs, serious TEAEs, related serious TEAEs, high-grade TEAEs, Grade 5 TEAEs, and TEAEs resulting in study treatment discontinuation will be similarly summarized. Summaries by worst reported severity for each event within a subject will also be provided.

At each level of summarization, a subject will be counted only once for each AE preferred term he/she experiences within that level (ie, multiple episodes of events with the same preferred terms will be counted only once).

All reported subject deaths will be summarized by treatment group, cause of death, and relationship to study treatment.

9.6.2. Laboratory Test Results

Laboratory test results will be summarized by treatment group to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

9.6.3. Other Safety Endpoints

Changes or shifts from baseline in vital signs, ECOG performance status, and QTc interval will be summarized by treatment group.

The number of subjects experiencing dose reduction, interruption/delay, and/or discontinuation due to an AE will be provided.

Concomitant medications will be standardized using the World Health Organization drug dictionary and summarized by class and preferred term.

9.7. Power and Sample Size

The study is designed to provide adequate power for analyses of both primary endpoints of PFS and OS comparing the experimental arm (cabozantinib + atezolizumab) with the control arm (sorafenib), and for the analysis of the secondary endpoint of PFS comparing single-agent cabozantinib with control arm. For the primary endpoints, a larger sample size is needed to provide reasonable power for OS than is required to evaluate PFS. As a result, if PFS were to be evaluated in the entire study sample, the PFS events may be biased toward shorter progression times. Thus, to allow longer, more robust PFS follow up among a smaller number of subjects, this study employs a “trial within a trial design” (Hessel et al 2016).

The total sample size was planned to be 740 subjects randomized in a 2:1:1 fashion: 370 to the experimental combination arm (cabozantinib + atezolizumab), 185 to the control arm (sorafenib),

and 185 to the single-agent cabozantinib arm. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects.

For primary PFS, a total of 257 events in the first 372 subjects randomized in a 2:1 ratio in the experimental and control arms (n=248 and 124, respectively; the PITT population) provide the study with 90% power for a 2-sided log-rank test with a 1% level of significance to detect a hypothesized true HR of 0.6. Assuming an exponential distribution of PFS, this corresponds with a 67% increase in median PFS from 3.6 months to 6.0 months. The minimum observed effect that would result in statistical significance for PFS is an HR of 0.71, a 41% improvement in median from 3.6 to 5.1 months. Interim analysis of the primary PFS endpoint is not planned.

For OS, a total of 368 deaths among all 555 subjects randomized in a 2:1 ratio in the experimental (n=370) and control arms (n=185) are required to provide 90% power to detect an HR of 0.69 using the log-rank test and a 2-sided significance level of 4%. Assuming an exponential distribution for OS, this corresponds to a 45% increase in median survival from 12.3 months to 17.8 months. The minimum observed effect that would result in statistical significance for the primary analysis of OS is an HR of 0.7942, a 26% improvement in median from 12.3 to 15.5 months.

For the secondary endpoint of PFS for the single-agent cabozantinib arm vs the control arm (sorafenib), a total of 283 events among all 370 subjects (185 per arm) in the single-agent cabozantinib and control arms provides the study with 85% power for a 2-sided log-rank test with a 1% level of significance to detect a hypothesized true HR of 0.65. Assuming an exponential distribution for PFS, this corresponds with a 53% increase in median PFS from 3.6 months to 5.5 months. The minimum observed effect that would result in statistical significance for PFS is an HR of 0.735, a 36% improvement in median from 3.6 to 4.9 months.

With an average accrual rate of 30 subjects per month it is estimated that it will take approximately 18.4 months to observe the required primary PFS events (16.5 months of subject accrual) and approximately 38 months to observe the required deaths for OS (25 months of subject accrual) to evaluate the primary endpoints in the combination and control arms. Assuming the same accrual rate, it is anticipated that it will take approximately 25 months to

observe the required secondary PFS events (25 months of subject accrual) to evaluate the secondary endpoint in the single-agent cabozantinib and control arms. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined. The Mainland China Extension Phase will not be expanded beyond 148 subjects.

An overview of the primary and secondary endpoints and operating characteristics is shown in Table 33:

Table 33: Summary of Endpoint Operating Characteristics

Accrual per month	30 subjects		
Randomization allocation	2:1 within Experimental and Control Arms		1:1 within Single-Agent Cabozantinib and Control Arms
Endpoint:	**PFS: Primary endpoint**	**OS: Primary endpoint**	**PFS: Secondary endpoint**
Power	90%	90%	85%
Alpha allocated (2-sided)	0.01	0.04	0.01
# of interim analyses (approximate information fraction)	0 (NA)	2 (33%, 66%)[a]	1 (67%)
Assumed median, control (months)	3.6	12.3	3.6
Assumed median, experimental (months)	6.0	17.8	5.5
Assumed HR	0.60	0.69	0.65
Number of events	257	368	283
N for analysis Population n1 vs n2	372 PITT Population 248 vs 124	555 ITT Population 370 vs 185	370 ITT Population 185 vs 185
Time to enroll (months)	16.5	25	25
Time to trigger event (months)	18.4	38	25

[a] Should the timing of the first interim analysis trend towards an information fraction much higher than expected (eg, due to faster-than-expected deaths or slower-than-expected PFS events), the plan for the interim analyses of OS may be modified (see Section 9.8).

China Subpopulation Sample Size: Up to 148 subjects from mainland China are planned to be enrolled (in the global and Mainland China Extension phases) in the study to meet a target of approximately 20% of the total sample size in the global enrollment (N=740). This population size is expected to be sufficient to allow evaluation of consistency in efficacy and safety in the China subpopulation compared with the global study per NMPA guidance. Analyses for the China subpopulation are described in Section 9.9.

9.8. Interim Analyses

The number of events required to evaluate OS is based upon assumptions currently available and provides high power to detect the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the trial early if the treatment benefit of the experimental arm is larger than expected, potentially allowing the new regimen to become available sooner to this patient population.

Two interim analyses of OS are planned at approximately the 33% and 66% information fractions based on a total alpha of 4%. However, if the null hypotheses are rejected for both the primary and secondary PFS endpoints, the 1% alpha for PFS will be reallocated to OS per the fallback method. As a consequence, the final OS analysis will employ critical values from the spending function at the 5% level. The alpha level of the interim analysis at 66% will be dependent on the timing of the interim analysis and the results of secondary PFS interim and final analyses. The second interim analysis of OS at 66% information fraction can be conducted at the overall 5% alpha level only if it occurs after the null hypothesis for the secondary PFS is rejected at the interim analysis.

Details and boundaries for these interim and the final analyses are shown in the table below:

	Critical Values for Testing OS					
OS alpha total	4.0%		4.96%		5.0%[a]	
OS analysis information fraction	Critical p-value	HR to reject	Critical p-value	HR to reject	Critical p-value	HR to reject
33%[b]	≤ 0.00011	≤ 0.478	NA[c]	NA[c]	≤ 0.0021	≤ 0.482
66%[d]	≤ 0.00867	≤ 0.701	≤ 0.01196	≤ 0.705	≤ 0.0120	≤ 0.705
100%	≤ 0.03728	≤ 0.794	≤ 0.04588	≤ 0.797	≤ 0.0463	≤ 0.797

HR, hazard ratio; NA, not applicable; OS, overall survival.

[a] Analyses of OS will be conducted at 5% alpha level only if the null hypotheses for both the primary and secondary PFS endpoints are rejected prior to testing OS.

[b] OS will not be tested at the 33% information fraction unless the null hypothesis for PFS has been rejected.

[c] The interim analysis at 33% information fraction will be conducted at 4% alpha level.

[d] The interim analysis at 66% information fraction will be conducted at 4% alpha level if it occurs prior to the secondary PFS analysis. It will be conducted at 4.96% alpha level if it happens after the null hypothesis for secondary PFS is rejected at the time of final analysis. It will be conducted at 5% alpha level only if the null hypothesis for secondary PFS is rejected at the interim analysis.

Rejection of the null hypotheses for OS at the first interim analysis at about 33% information is not expected: it is designed primarily as an administrative analysis, expected to coincide with the primary analysis of PFS, and will be performed only if the null hypothesis for PFS is rejected.

Should the timing of the first interim analysis (IA1) of OS trend towards an information fraction much higher than expected (eg, due to faster-than-expected deaths or slower-than-expected PFS events), the interim analyses of OS will be conducted as follows:

OS IA1 IF	**Proceed as**	**Rationale**
< 50%	perform IA1 and IA2 as planned above	similar conditions to original plan
50 to < 66%	• perform IA1 at time of primary PFS, irrespective of whether PFS null hypothesis is rejected or not • Conduct IA2 at 80% IF (instead of 66%)	• Higher than expected information for OS negates administrative nature of the analysis. • Preserves two interim analyses as planned with reasonable intervals between them
≥ 66%	perform a single interim analysis at 66% IF, irrespective of timing or results of primary PFS analysis.	Information fraction meets or exceeds that of planned analysis at 66%

IA1, first interim analysis; IA2, second interim analysis; IF, information fraction; OS, overall survival

An interim analysis of secondary PFS is planned contemporaneously with the primary PFS analysis and will be conducted only if the null hypothesis for primary PFS is rejected. It is anticipated to be at approximately 67% information fraction based on a total alpha of 1%. At this fraction, the critical p-value is 0.0096, and the maximum HR to reject the null hypothesis is 0.626.

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of secondary PFS and OS will depend upon the actual information fraction at the time of the analyses. Descriptive supportive analyses will be provided at the planned information fraction at the time of the analyses.

If a null hypothesis is rejected for a given endpoint at interim analysis (secondary PFS or OS), no subsequent testing of that endpoint will be performed.

Interim analysis of primary PFS and futility analyses of PFS or OS are not planned.

9.9. Analysis Methodology for China Subpopulation

The primary scope of the China subpopulation analysis is to allow evaluation of consistency in efficacy and safety with the global study population per NMPA guidance. Since the China subpopulation is not powered to demonstrate statistical significance in terms of efficacy, no formal hypothesis testing will be performed. All data summaries for the China subpopulation (to include all subjects from China from the global and Mainland China Extension phases) will be descriptive. The safety and efficacy data in the China subpopulation will be analyzed separately for the same endpoints using the same analysis methods as for the global population. The analyses for this subpopulation will be performed when the data are of sufficient maturity to allow evaluation of consistency in efficacy and safety.

Details of the planned summaries will be provided in a separate SAP for the China subpopulation that will be finalized before the last subject is randomized in the China.

10. OTHER ANALYSES

10.1. Pharmacokinetic Analyses

The plasma concentration of cabozantinib will be analyzed by the designated laboratory using a validated bioanalytical method. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit. Where appropriate, these data may be combined with data from other studies as part of a meta-analysis (ie, population PK analysis). The effect of cabozantinib exposure on biomarkers, clinical safety parameters (eg, selected AEs), or clinical response may also be explored.

Serum concentrations of atezolizumab will also be measured and summarized. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit.

10.2. Immunogenicity Analyses

Results of anti-drug antibody (ADA) testing (ie, immunogenicity testing) will be summarized overall as the number of subjects with ADA at any time point. The association between human ADA incidence, PK, and efficacy and/or safety outcomes may be explored.

10.3. Biomarker Analyses

Analyses may include MET and PD-L1 expression and other analyses (eg, tumor mutational burden) with clinical response.

11. DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the Investigator's records by the study monitor (source document verification) and by the maintenance of a drug-dispensing log by the investigator. Authorized study site personnel will enter data directly into a computerized CRF database (ie, electronic data capture [EDC] system). Study databases will be subject to electronic and manual quality assurance procedures.

12. STUDY COMMITTEES

12.1. Executive Safety Committee (ESC)

The Sponsor's Executive Safety Committee (ESC) provides safety oversight over periodic and ongoing reviews on product safety data and blinded study data (through a Safety Management Team). The ESC provides the company position and actions for all safety aspects of the company's product to protect patient safety and public health. The ESC is managed and chaired by the Head of Drug Safety, and includes the following other members: Chief Medical Officer, Head of Clinical Development, Head of Regulatory Affairs and qualified representatives of other functional groups as appropriate.

12.2. Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in oncology.

This IDMC will convene regularly, including a safety assessment after a total of 50 subjects have been randomized and followed for at least 6 weeks. The primary responsibilities of the IDMC are to:

- Review the accumulating safety data on a regular and an ad hoc basis
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety and efficacy data

Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings. To allow the evaluation of safety in the context of potential benefit, OS data (including Kaplan-Meier curves) may be reviewed by the IDMC at the time of safety summary reviews. The IDMC will have access to subjects' individual treatment assignments.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.

The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to the Sponsor's senior management.

Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate IDMC charter.

12.3. Clinical Steering Committee (CSC)

The Clinical Steering Committee of the study consists of physicians who have an expertise in treating patients with HCC. The CSC will provide critical scientific guidance including, but not limited to, protocol design and implementation and interpretation of clinical study results.

12.4. Blinded Independent Radiology Committee (BIRC)

A BIRC will be established to evaluate tumor scans and prior radiation history data of trial subjects in a central, blinded, and independent fashion (see also Section 5.8.6.4). The BIRC will be comprised of board-certified radiologists who will determine radiographic response and progression following randomization. Additional imaging results may be requested by the Sponsor for BIRC review.

Primary analyses of radiographic study endpoints will be based upon BIRC assessments.

Additional details regarding BIRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the BIRC Charter.

13. ETHICAL ASPECTS

13.1. Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent version of the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

13.2. Informed Consent

Sample ICFs will be supplied to each site. The Sponsor or its designee must review any proposed deviations from the sample ICF. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, the ICF will be provided in a certified translation of the subject's language.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, will be given a copy of the revised form, and must give their consent to continue in the study.

If a subject requests to discontinue study treatment and/or withdraws study consent, the Investigator must establish the specific nature of the subject's request, as described in Section 3.5.2.

13.3. Institutional Review Board/ Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The Investigator will send a letter or certificate of IRB/ EC approval to the Sponsor (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

13.4. Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all research samples. If a subject requests destruction of their tissue and blood samples, the Sponsor will make every attempt to destroy the samples. The Sponsor will notify the Investigator in writing that samples have been destroyed, if requested by the subject.

14. CONDITIONS FOR MODIFYING THE PROTOCOL

If deemed necessary, protocol modifications will be prepared, reviewed, and approved by the Sponsor representatives.

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 (eg, change in monitor or change of telephone number).

15. CONDITIONS FOR TERMINATING THE STUDY

The Sponsor reserves the right to terminate the study, and Investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, the Sponsor and the Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

16. STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORD KEEPING

16.1. Investigator's Files and Retention of Documents

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

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

Subjects' clinical source documents to record key efficacy and safety parameters independent of the CRFs include the subjects' hospital/ clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, x-ray, pathology and special assessment reports; signed ICFs; consultant letters; and subject screening and enrollment logs.

The Investigator must keep these two categories of documents on file for the maximum period required by applicable regulations and guidelines, institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. After that period, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirements at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

16.2. Source Documents and Background Data

Upon request, the Investigator will make available for review by the Sponsor any required background data from the study documentation or clinic records. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

16.3. Audits and Inspections

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

16.4. Case Report Forms

The term "case report form" (CRF) includes electronic data capture screens or forms for studies that utilize electronic data capture. For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and required by the CRFs are to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical examinations, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the Investigator's institution or medical practice standard of care. Data from assessments associated with the follow-up of AEs are to be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments are to remain in the subject's medical record and are not to be recorded on CRFs unless specifically requested.

The CRF casebook must be completed and signed by the Investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

The Sponsor's data management personnel (or designees) may, in specific circumstances, modify study data – without changing the meaning of the data – to ensure the dataset complies with conventions required for successful data extract, thesaurus coding, or uniform reporting and does not cause these processes to fail. Examples of these administrative changes include:

- Substitution of non-standard ASCII characters (codes 128-255) or deletion of carriage returns (code 13) that are incompatible with the SAS XPT file format (eg, accented letters replaced with non-accented ones; e for é)
- Splitting multiple verbatim AE terms into multiple records (eg, "nausea and vomiting" to separate records for "nausea" and "vomiting")

- Reformatting failed eligibility criteria numbers for uniformity or specificity (eg, changing “2 a” to “2A”; or “2” to “2A” based on corroborating evidence from the clinical database)

- Changing cause of death from “unknown” to “unknown cause of death” to facilitate coding in the MedDRA thesaurus

Such changes follow a pre-defined documented process and can be clearly identified in the database audit trial. By participating in this study, investigators agree that such administrative changes are permissible without their specific prior approval. A list of all specific changes made can be provided to investigators upon request at any time.

17. MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor is to have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

18. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

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

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In the event that the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of the investigator(s) or other representatives of the study site(s) as named author(s) shall be determined in accordance with Sponsor policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

20. COMPLIANCE WITH DATA PROTECTION LAWS

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation ([EU] 2016/679) and any national implementing laws, regulations and secondary legislation, as amended or updated from time to time. The Sponsor shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law (which may include consent from the subject or another lawful basis).

21. REFERENCES

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APPENDICES

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety and patient reported outcomes are to occur corresponding with study weeks (eg, Week 5 Day 1 [W5D1]) which are fixed from Week 1 Day 1 (W1D1) defined as the date of the first dose of study treatment. W1D1 should occur within 3 days after randomization. All assessments for radiographic endpoints (CT, MRI) as well as HRQOL (ie, EQ-5D-5L) will be scheduled based on W1D1 and are to be performed even for subjects randomized but never treated. For such subjects, W1D1 is defined as the date of randomization.

In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal visit day, unless otherwise indicated. For subjects in the combination arm, required safety assessments may occur outside the protocol defined windows due to safety-driven delays in atezolizumab administration and will not be considered protocol deviations as long as required safety assessments are performed at least every 3 weeks (± 3 days). See the CRF completion guidelines for instructions on how to enter study data in such circumstances.

If study treatment is held or missed after W1D1, assessments should continue following the schedule described below.

Unscheduled safety assessments or phone calls, if required as defined in the protocol, are to be performed weekly (or more frequently) as clinically indicated. See Section 5.7 for further details.

Special accommodations during the global COVID-19 pandemic are described in Appendix M.

Appendix A: Schedule of Assessments

Assessment:	Pre-randomization	Post-randomization							
	Screening[a] (before randomization)	W1D1 (Should occur ≤ 3 days after randomization)	(± 3 Days) W4D 1	(± 3 Days) W7D1	(± 3 Days) W10D 1	(± 3 Days) W13 D1	After Beginning of Week 13 (± 3 days)	First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)	Second Post-Treatment Follow Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)
Informed consent (Section 5.1)	X[b]								
Demographics, medical and cancer history (Section 5.8.1)	≤ 28 days	X							
Physical examination + weight (Section 5.8.2)[k]	≤ 14 days (with height)	X (prior to first dose; symptom-	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
Vital signs (Section 5.8.3)[k]	≤ 14 days	X (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
Serum AFP (Section 5.8.7)[k]	≤ 14 days	X (prior to first dose)	X	X	X	X		X	X
ECOG performance status (Section 5.8.2)[k]	≤ 14 days	X (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
12-lead ECG (Section 5.8.4)[c,k]	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	Every 12 weeks (W25D1, W37D1, etc)	X	
Hematology by central lab[e,k] (Section 5.8.5)	≤14 days	X[d] (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
Chemistry by central lab[e,k] (Section 5.8.5)	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
PT/INR and PTT by central lab (Section 5.8.5)[e,k]	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	

Assessment:	Pre-randomization	Post-randomization							
			(± 3 Days)						
	Screening[a] (before randomization)	**W1D1 (Should occur ≤ 3 days after randomization)**	**W4D 1**	**W7D1**	**W10D 1**	**W13 D1**	**After Beginning of Week 13 (± 3 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)**	**Second Post-Treatment Follow Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)**
Urinalysis by **local** lab[e,k] (Section 5.8.5)	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
Urine chemistry incl. UPCR by central lab (Section 5.8.5)[k]	≤ 14 days (local labs allowed if needed to meet planned randomization date)	X[d] (prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
24 hour urine by **local** lab (Section 5.8.5)[k]		Perform at the discretion of the Investigator based on increases in UPCR from routine assessments							
Serum or urine pregnancy test by **local** lab (Section 5.8.5)[k]	≤ 7 days (serum)	X[d] (serum: prior to first dose)	X	X	X	X	Every 3 weeks (W16D1, W19D1, etc)	X	
Thyroid function test by central lab (Section 5.8.5)[e,k]	≤ 14 days	X[d] (prior to first dose)	X	X		X	Every 6 weeks (W19D1, W25D1, etc)	X	
Follicle stimulating hormone by central lab[f,k] (Section 5.8.5)	≤ 14 days								
Tumor tissue (Section 5.8.12)	X[g]		An optional biopsy can be collected approximately 6 weeks after the first dose of study treatment; other time points may be acceptable provided the tumor sample is collected prior to progressive disease. Treatment with cabozantinib or sorafenib must be interrupted for at least 5 days before optional tumor biopsies are performed and may not be reinitiated until complete wound healing has occurred (at least 10 days).						

Assessment:	Pre-randomization	Post-randomization							
			(± 3 Days)						
	Screening[a] (before randomization)	**W1D1 (Should occur ≤ 3 days after randomization)**	**W4D 1**	**W7D1**	**W10D 1**	**W13 D1**	**After Beginning of Week 13 (± 3 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)**	**Second Post-Treatment Follow Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)**
Diagnosis of HCC by imaging[j] (optional at radiology-accredited sites) (Section 5.8.6.1)	≤ 28 days								
Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis** (Section 5.8.6)	≤ 28 days	CT of CAP or CT chest and MRI of abdomen/pelvis will be performed in all subjects at screening and then every 6 weeks (± 7 days) after randomization through Week 49. After Week 49, these assessments will be performed every 12 weeks (± 7 days). Tumor assessments should continue on the protocol-defined schedule regardless of whether study treatment is given, reduced, held or discontinued until a criterion for ending radiographic assessment is met (Section 5.8.6). The same imaging modality will be used for subsequent tumor assessments after randomization. For subjects who discontinue study treatment before Investigator-determined radiographic disease progression, tumor assessments are to continue per the protocol defined schedule until Investigator-assessed radiographic disease progression per RECIST 1.1. For subjects who continue to receive study treatment after Investigator-assessed radiographic disease progression because of Investigator-assessed clinical benefit which outweighs the potential risks, tumor assessments are to continue per the protocol defined schedule until study treatment is permanently discontinued.							
Tumor assessment: MRI/CT **Other Sites** (Section 5.8.6)	≤ 28 days	All other known or suspected sites of disease, including in the brain or bone, are to be imaged by CT/MRI at screening (prior to randomization). Any lesions identified, including bone lesions with a soft tissue component, are to be followed at subsequent tumor assessments as described for CAP above using the same modality as at screening. New suspected lesion sites identified after randomization, including suspected sites of bone or brain lesions, should be assessed by CT/MRI. MRI is the preferred method for brain lesion assessment. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. Tumor assessments should continue on the protocol-defined schedule regardless of whether study treatment is given, reduced, held or discontinued until a criterion for ending radiographic assessment is met (Section 5.8.6). For subjects who discontinue study treatment before investigator-determined radiographic disease progression, tumor assessments are to continue per the protocol defined schedule until investigator-assessed radiographic disease progression per RECIST 1.1. For subjects who continue to receive study treatment after investigator-determined radiographic disease progression because of investigator-assessed clinical benefit which outweighs the potential risks, tumor assessments are to continue per the protocol defined schedule until study treatment is permanently discontinued.							

Assessment:	Pre-randomization	Post-randomization							
			(± 3 Days)						
	Screening[a] (before randomization)	**W1D1 (Should occur ≤ 3 days after randomization)**	**W4D 1**	**W7D1**	**W10D 1**	**W13 D1**	**After Beginning of Week 13 (± 3 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)**	**Second Post-Treatment Follow Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)**
HRQOL-EQ-5D-5L[h] (Section 5.8.8)	≤ 14 days		Every 6 weeks after W1D1 (eg, W7D1, W13D1, etc). These assessments are to be performed regardless of whether study treatment is given, reduced, held or discontinued until the date of the last tumor imaging assessment as described in Section 5.8.6. Consequently these assessments may be required in the Post Treatment Period for some subjects.						
Cabozantinib PK plasma samples[i] (Section 5.8.10)		X (prior to first dose)	X predose	X predose	X predose	X predose			
Atezolizumab PK serum samples (Section 5.8.10)		X (prior to first dose)	X predose	X predose	X predose	X predose		X	X
Immunogenicity blood sample (Section 5.8.11)		X (prior to first dose)				X	W25D1	X	X
Pharmacogenetic blood sample (Section 5.8.12)		X (prior to first dose)							
Immune cell profiling blood sample (Section 5.8.12)		X (prior to first dose)		X		X			
Cell and/or plasma pharmacogenomic samples (Section 5.8.12)		X (prior to first dose)	X	X	X	X		X	
Plasma biomarker samples (Section 5.8.12)		X (prior to first dose)	X	X	X	X		X	
Concomitant medication (Section 7)	Document concomitant medication taken from 28 days before randomization through 30 days after the date of the decision to discontinue study treatment								

Assessment:	Pre-randomization	Post-randomization							
	Screening[a] (before randomization)	W1D1 (Should occur ≤ 3 days after randomization)	(± 3 Days) W4D 1	W7D1	W10D 1	W13 D1	After Beginning of Week 13 (± 3 days)	First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)	Second Post-Treatment Follow Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)
Adverse events (Section 8)	Document new or worsening AEs from first dose (SAEs from informed consent) through 30 days (100 days for SAEs and AESIs) after the date of the decision to permanently discontinue study treatment. Related SAEs should be documented at any time. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. On W1D1 AEs will be documented pre- and post-dose. Related AEs leading to study treatment discontinuation, AESIs (regardless of causality), and related SAEs are to be followed until resolution, ≤ Grade 2 severity, or determination by the investigator that the event is stable or irreversible (see Section 8.3).								
Healthcare Resource Utilization (Section 5.8.9)		Collection of hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions from randomization through the 100-Day Post-Treatment Follow-up Visit (FU-2).							
Cabozantinib dosing (Sections 6.2.1, 6.2.3, 6.2.4, and 6.2.5)		Experimental Arm: Cabozantinib tablets given on W1D1 after atezolizumab infusion. Taken once daily at home thereafter until study treatment is discontinued. Single-Agent Cabozantinib Arm: Cabozantinib tablets given in the clinic on W1D1. Taken once daily at home thereafter until study treatment is discontinued.							
Sorafenib dosing (Sections 6.2.2, 6.2.4, and 6.2.6)		Control Arm: First sorafenib dose (tablets) given on W1D1 in the clinic. Taken twice daily at home thereafter until study treatment discontinued							
Atezolizumab dosing (Section 6.1.1.2)		Doses of atezolizumab will be administered intravenously at the clinic by infusion every 3 weeks (± 2 days). Atezolizumab dosing days may not necessarily align with safety assessment visits.							
Dispense/return of oral study drug and compliance accounting (Sections 6.4 and 6.5) [l]		X	X	X	X	X	Every 3 weeks (W16D1, W19D1 etc)		
Additional anticancer treatment and survival status (Section 5.8.13)		All treated subjects will be contacted at each post-treatment visit, including FU-1, FU-2, and every 12 weeks (± 14 days) after FU-2 visit until death. Any subjects who are randomized but not treated will be contacted every 12 weeks post-randomization until death							

[a] Results of screening assessments must be reviewed before randomization to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to randomization, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies.

[c] Additional ECGs should be performed if clinically indicated.

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 14 days (7 days for pregnancy test) prior to first dose (W1D1), this assessment does not need to be performed on W1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[e] Serum chemistry, hematology, coagulation, and urinalysis laboratory samples must be collected, and results must be reviewed within 72 hours before any atezolizumab infusion administered on study. If the subject has symptoms indicative of a thyroid function disorder, thyroid function test results are to be reviewed prior to

administering atezolizumab. See Section 5.8.5 and the Laboratory Manual for more detailed information on laboratory assessments and when local assessments may be performed in lieu of central assessments for serum chemistry, hematology, coagulation, and thyroid function prior to atezolizumab administration.

[f] For women under the age of 55 years to confirm menopause as needed.

[g] Archival tumor tissue (most recently obtained) will be provided, if available. If archival tissue and histological/cytological confirmation of disease are not available, a tumor biopsy may be collected during screening with subject consent

[h] HRQOL forms should be administered and collected prior to any other study-related activities for scheduled visits. Questionnaires should be completed prior to the clinic visit or if completed on the day of the visit prior to seeing the study site personnel.

[i] For each on-treatment visit, the PK sample should be collected approximately 8 or more hours after the previous dose of cabozantinib, and if cabozantinib will be administered on that day, should be collected prior to cabozantinib administration. The investigator will ask the subject for the date and time of the most recent prior dose of cabozantinib and this information will be recorded on the appropriate CRF page.

[j] Clinical diagnosis of HCC by multiphase imaging using CT or MRI in subjects with cirrhosis for eligibility may be performed at the sites accredited by the Sponsor. Diagnostic scans may be used for screening if they meet the criteria described in Section 5.8.6.2. Refer to the guidance on diagnosis of HCC in cirrhotic patients by imaging in Section 5.8.6.1.

[k] For subjects in the combination arm, required safety assessments may occur outside the protocol defined windows due to safety-driven delays in atezolizumab administration and will not be considered protocol deviations as long as required safety assessments are performed at least every 3 weeks (± 3 days). See the CRF completion guidelines for instructions on how to enter study data in such circumstances

[l] In exceptional circumstances (eg, COVID-19 pandemic), alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations.

Appendix B: Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen (ie, cabozantinib + atezolizumab) within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.5.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per institutional standard of care and guidance from the Sponsor. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs, and other reportable events (pregnancy, DILI and medication errors with sequelae) is to continue per protocol (Section 8.2).

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse events of special interest (AESIs)
- Adverse events, whether serious or not, leading to study treatment discontinuation
- Adverse events, whether serious or not, leading to study treatment dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2) at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the Post-Treatment Follow-up Visits. Upon initiation of the Maintenance Phase, no further follow up is required for any subject who has completed the FU-1 and FU-2 Visits.

Study drug accountability is to continue as described in Section 6.5.

See the Maintenance Phase Schedule of Assessments below. To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency but must be frequent enough to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into CRFs. Study central laboratory samples are not to be obtained. Local laboratory results are not to be submitted to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central ECG vendor.

Appendix B: Schedule of Assessments: Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment is Permanently Discontinued)	**Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2)**
Study drug accountability	Every time study drug is dispensed	✓[a]
Study treatment	Atezolizumab: Once every 3 weeks; Cabozantinib: Daily OR Sorafenib: Daily. Study treatment may continue until a criterion for discontinuation is met (Section 3.5).	-
Safety evaluation: *Clinical examination and local laboratory assessments per SOC*	Frequency per standard of care	✓[a]
Reporting of SAEs, AESIs, and other reportable events (DILI, pregnancy, and medication errors with sequelae)	Submit reports to Sponsor per Section 8.2	
Reporting of AEs: • leading to study treatment discontinuation • leading to study treatment dose modification (ie, causing study treatment to be withheld or reduced)	Submit reports to Sponsor per the same process as for reporting SAEs per Section 8.2 SAE reporting timeline requirements do not apply to non-serious events reported in these categories	
Tumor assessments: *Imaging methods per SOC*	Frequency per standard of care	-

AE, adverse event; DILI, drug-induced liver injury; FU-1, 30-Day Post-Treatment Follow-up Visit; FU-2, 100-Day Post-Treatment Follow-up Visit; SAE, serious adverse event; SOC = standard of care
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central ECG vendor.
[a] Subjects should return all unused study medication and undergo a safety evaluation per standard of care.

Appendix C: Performance Status Criteria

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

Appendix D: Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects 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 include:

- Subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low
- Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone, controlled Type 1 diabetes mellitus and on an insulin regimen, or asthma that requires intermittent use of bronchodilators
- Subjects with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis)

Caution should be used when considering atezolizumab for subjects who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent.

Contact the Sponsor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Crohn disease		

Appendix E: Response Evaluation Criteria in Solid Tumors Version 1.1 (also known as RECIST 1.1)

Adapted from Eisenhauer et al 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

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

- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable. Following a time point response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are generally not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed. Following a time point response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Lesions with prior local treatment

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the

image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Positron emission tomography will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study.

Bone scans may be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm results of bone scans. Preferred method for confirmation is MRI.

Tumor Markers: Tumor markers (eg, AFP) may be evaluated for changes in response to treatment but will not be used to determine PD in this study.

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or SD in order to differentiate between response (or stable disease) and PD.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is reduced, interrupted, delayed, or discontinued until a protocol-defined criterion for ending radiographic assessments is met (see Section 5.7.6.2).

At baseline, tumors and lymph nodes are classified and documented as target or nontarget lesions per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases'). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' should be included in source documents.

For target lesions, measurements should be taken and recorded in metric notation.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a 'new' cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression cannot be based solely on bone scan findings. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary. These CT/MRI findings will be used for the determination of progression.

TIME POINT RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions).

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR / Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should normally not trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (NA)	No non-target lesions identified at screening.
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). Note: The appearance of one or more new lesions on CT or MRI scan is considered progression if these findings are unequivocally not due to a change in the imaging technique or modality. On bone scan, new lesions are not sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm results of bone scan. Preferred method for confirmation is MRI.
No	No new lesions present at follow-up.
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Time Point Response			
Target Lesion TPR	**Non-target lesion TPR**	**New lesion TPR**	**Overall TPR**
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Any except PD	No	UE
PD	Any	No or Yes	PD
Any	PD	No or Yes	PD
Any	Any	Yes	PD**
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE	No	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TPR, time point response; UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior or subsequent time point (ie, confirmation requirement are not considered when assigning time point responses).

* Subjects with an overall response of CR or PR must have a follow-up tumor assessment performed no less than 4 weeks after the criteria for response are first met (this may be performed at the next scheduled tumor assessment). However, the presence, absence, or status at this follow-up assessment is not considered when assigning a time point response at prior time points.

** If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the subject's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the subject's tumor had reached a CR status and the lesion reappeared, then the subject would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response.

Furthermore, in order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the investigator should have a follow-up tumor assessment no less than 4 weeks after the initial PD criteria were met. This may be performed at the next scheduled tumor assessment. However, the presence, absence, or status at this follow up assessment is not considered when assigning a time point response at prior time points.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For subjects with an overall response of PR or CR at a given time point, a follow-up tumor assessment must be performed no less than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled tumor assessment.

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the investigator should have a follow-up tumor assessment no less than 4 weeks after the initial PD criteria were met. This may be performed at the next scheduled tumor assessment.

However, the presence, absence, or status at these follow-up assessments is not considered when assigning a time point response at prior time points.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

Appendix F: List of Strong Inducers and Inhibitors of CYP3A4

Cabozantinib is a CYP3A4 substrate (Section 7.3.1 Potential drug interactions with cabozantinib).

Chronic co-administration of cabozantinib with drugs known to be strong inducers of the CYP3A4 family may decrease cabozantinib concentrations and therefore should be avoided during treatment with cabozantinib. St. John's Wort (Hypericum perforatum) is also known to be an inducer of CYP3A4 and should be avoided.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family may increase cabozantinib concentrations and should be avoided during treatment with cabozantinib. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided during treatment with cabozantinib.

Strong Inhibitors of CYP3A4	Strong Inducers of CYPA4
Antivirals Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Indinavir Lopinavir Nelfinavir Ombitasvir Paritaprevir Ritonavir Saquinavir Telaprevir Tipranavir **Anti-Fungals** Itraconazole Ketoconazole Posaconazole Voriconazole **Antibiotics** Clarithromycin Telithromycin Troleandomycin Conivaptan Diltiazem Grapefruit juice Idelalisib Nefazodone	Carbamazepine Efavirenz Enzalutamide Erythromycin Mitotane Modafinil Nevirapine Oxcarbazepine Phenytoin Rifampin St. John's Wort

This table is not all-inclusive. Please refer to the FDA website for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

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

Appendix G: Infusion-Related Reaction and Cytokine Release Syndrome Guidelines

Event	Management Guideline
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, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2:[a] Fever[b] with hypotension not requiring vasopressors **and/or** 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 (eg, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • 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, and contact Sponsor. • 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, anti-pyretics, 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 Sponsor.

Grade 3:[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Sponsor.[f] • 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 (eg, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • 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 and in consultation with the Sponsor.
Grade 4:[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Sponsor.[f] • 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 (eg, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator and in consultation with the Sponsor. • 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 for CRS. NCI CTCAE (version 5.0) 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 ≥ 38°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, anti-pyretics, 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] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to rechallenge with atezolizumab should be based on investigator's assessment of benefit-risk, and documented by both the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, 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.

[g] Refer to Riegler et al (2019) for information on experimental treatments for CRS.

Appendix H: Methods of Contraception

In Inclusion Criterion 12 (Study Synopsis and Protocol Section 4.2):

Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and for 5 months after the last dose of study treatment. Such methods include:

- Placement of an intrauterine device (IUD)
- Placement of an intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (the reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the subject)
- Combined (estrogen- and progestogen-containing) hormonal contraception*:
    - Oral
    - Intravaginal
    - Dermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation*:
    - Oral
    - Injectable
    - Implantable

* The effect of cabozantinib on the PK of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as "effective methods of contraception," they should be used together with another method.

Furthermore, male subjects must refrain from donating sperm and are required to use condoms in order to avoid transmission of study treatment in semen for the duration of study treatment and through 5 months after their last dose of study treatment.

Appendix I: Barcelona Clinic Liver Cancer (BCLC) Staging and Treatment Strategy

Source: Forner et al 2018

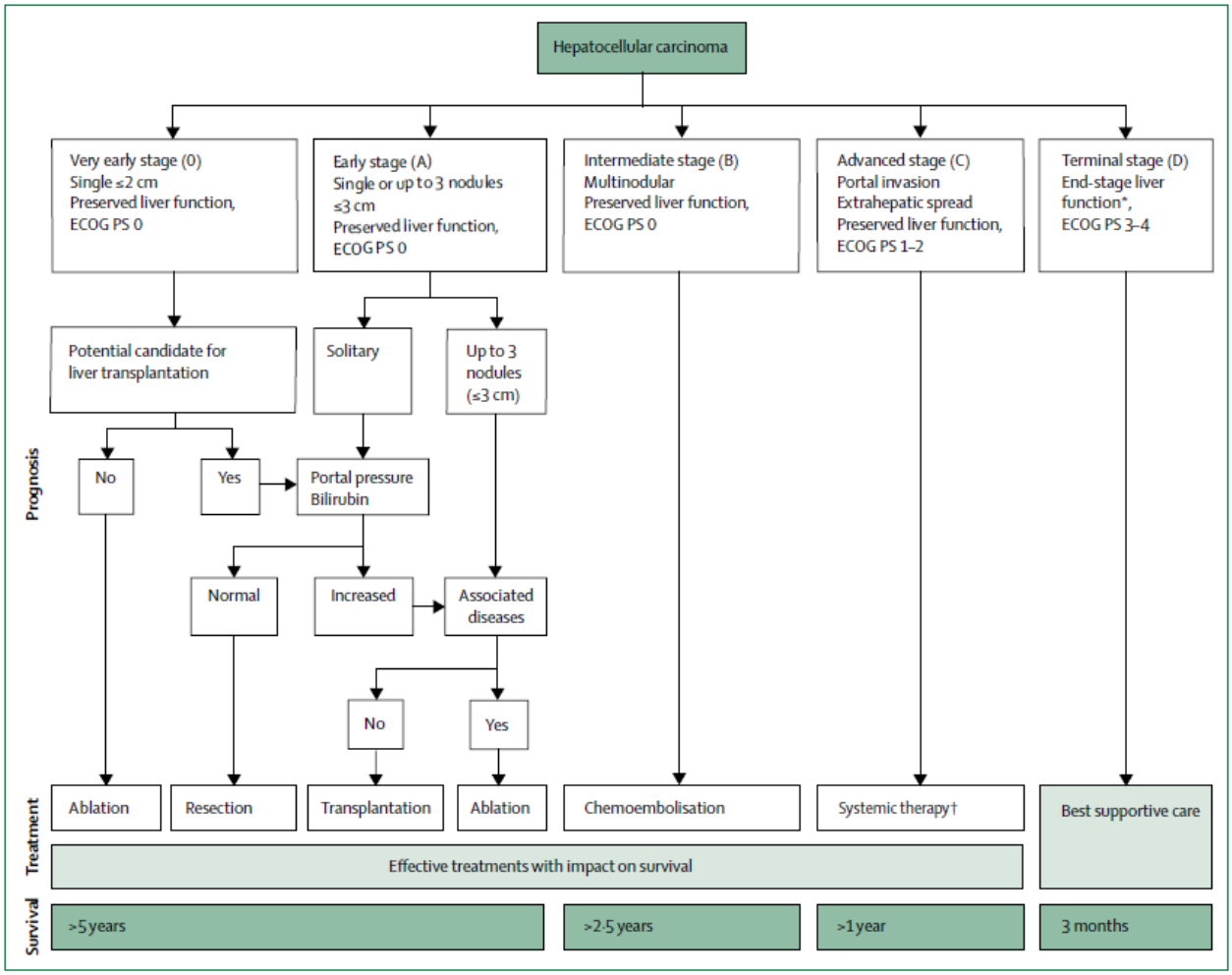


Figure 2: **Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy**
The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Note that liver function should be evaluated beyond the conventional Child-Pugh classification or the Model of End-stage Liver Disease (MELD) score. None of them serves to properly gauge the liver function status, and this evaluation should take into account biochemistry parameters as well as the compensated or decompensated status of the patient. Preserved liver function includes a group of patients with different degrees of liver function reserve that has to be carefully evaluated. For most treatment options, compensated liver disease (Child-Pugh stage A without ascites) is required to obtain optimal outcomes. The sole option that could be applied irrespective of liver function is liver transplantation. ECOG PS=Eastern Cooperative Oncology Group Performance Status. *Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation. In these patients, hepatocellular carcinoma might become a contraindication if it exceeds enlistment criteria. †Currently, sorafenib followed by regorafenib has been shown to be effective. Lenvatinib has been shown to be non-inferior to sorafenib, but no second-line option after lenvatinib has been explored.

Appendix J: Child-Pugh Scoring System

Modified Child-Pugh classification of severity of liver disease (Garcia-Tsao 2007) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	none	mild/moderate (diuretic-responsive)	tense (diuretic-refractory)
Total bilirubin, mg/dL	< 2	2-3	> 3
Albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.7	1.7-2.3	> 2.3
Encephalopathy	none	Grade 1-2 (or precipitant-induced)	Grade 3-4 (chronic)

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

Grade	**Points**	**1-year survival**	**2-year survival**
A: well-compensated disease	5–6	100%	85%
B: significant functional compromise	7–9	80%	60%
C: decompensated disease	10–15	45%	35%

Appendix K: Collection, Follow-Up, and Documentation Requirements for AEs, AESIs, and SAEs

All adverse events (AEs) that are not serious and not AESIs (AEs of special interest; Table 31) that start or worsen after the first dose of study treatment through the 30-day post-treatment follow-up visit (FU-1) visit are to be entered into the electronic CRF data capture system (EDC). Such events continuing at the FU-1 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes. These events do not require a Drug Safety SAE Form to be completed.

Additional requirements apply to the following events:

- All serious adverse events (SAEs) that are judged by the investigator to be not related to study treatment that start or worsen after the subject's initial informed consent through the 100-day post-treatment follow-up visit (FU-2) visit are to have a Drug Safety SAE Form completed. Such events continuing at the FU-2 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes.
- All AEs leading to study treatment discontinuation that are judged by the Investigator to be related to study treatment that are continuing at the FU-2 visit are to be followed by the Investigator until resolution, defined as: fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required. If serious, the requirements for related SAEs apply.
- All AESIs (regardless of seriousness) that start or worsen after the subject's initial informed consent through the FU-2 visit are to have a Drug Safety SAE Form completed and be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution, with evidence of resolution provided on updates to the Drug Safety SAE Form. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.
- All SAEs that are judged by the investigator to be related to study treatment that start or worsen at any time after the subject's initial informed consent are to have a Drug Safety SAE Form completed. Such events that occur prior to the FU-2 visit are to be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution, with evidence of resolution provided on updates to the Drug Safety SAE Form. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.

Summaries of the event surveillance (Table K-1) and follow-up requirements (Table K-2) are shown in the following page.

Table K-1: Requirements for Documenting the Incidence of AEs, SAEs and AESIs:

Event type	Event surveillance period (inclusive):			
	EDC CRF[a]		Drug Safety SAE Form	
	Period start	Period stop	Period start	Period stop
AE: nonserious, non-AESI	first dose	FU-1	NA	NA
SAE: not related	IC	FU-2	IC	FU-2
Related AE leading to study treatment discontinuation	first dose	EOT date	NA (if nonserious)	NA (if nonserious)
AESI: nonserious (AESIs: irAEs, potential DILI, Other; Table 31)	IC	FU-2	IC	FU-2
Related SAE	IC	FU-2	IC	ever

AE, adverse event; AESI, adverse event of special interest (Table 31); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 days after EOT date; FU-2, follow-up visit 100 days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

Table K-2: Requirements for Following up on Events Documented and Reported as Defined in Table L-1

Event type	Event follow-up requirements				
	If ongoing at…	…follow until…	…and document following on:		
			Source documents	EDC CRF	Drug Safety SAE Form
AE: nonserious, non-AESI	FU-1	NA	status at FU-1	status at FU-1	NA
SAE: not related, non-AESI	FU-2	NA	status at FU-2	status at FU-2	status at FU-2
Related AE leading to study treatment discontinuation	FU-2	Resolution[b]	evidence of resolution	status at FU-2	NA (if nonserious)
AESI: regardless of seriousness (AESIs: irAEs, potential DILI, Other; Table 31)	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution
Related SAE	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution

AE, adverse event; AESI, adverse event of special interest (Table 31); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 days after EOT date; FU-2, follow-up visit 100 days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

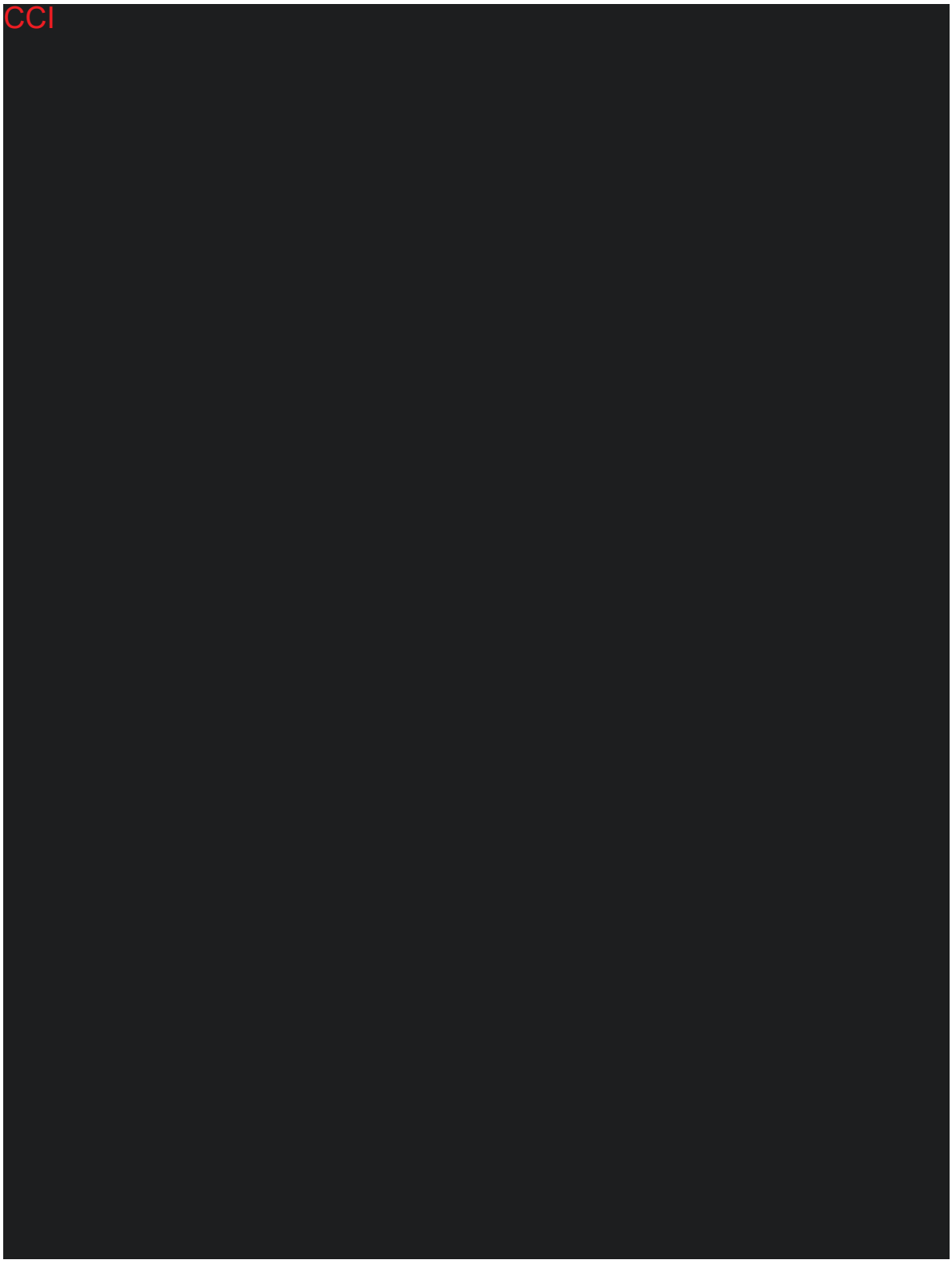
[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

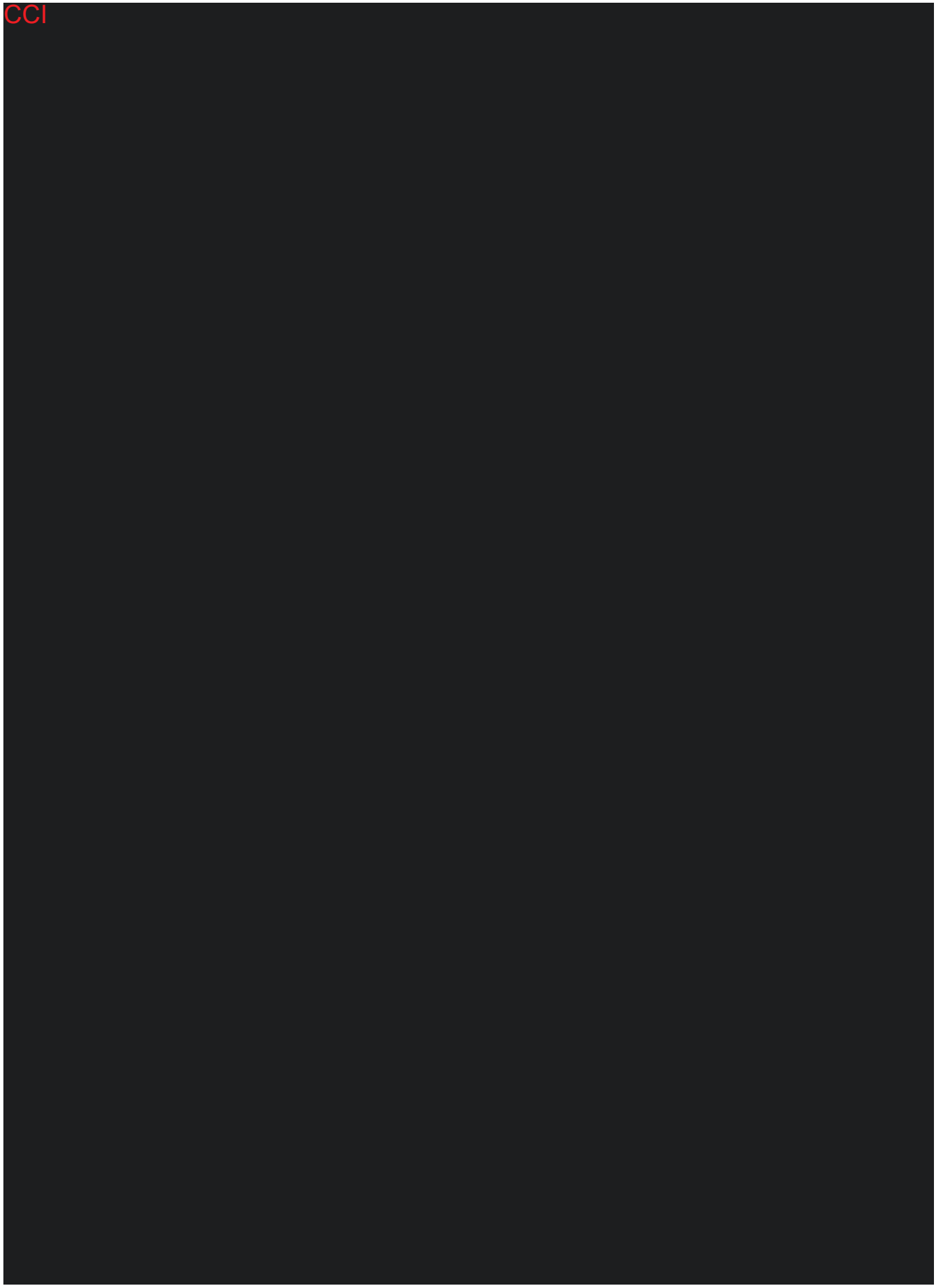
[b] Defined as: AE is fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator

Appendix L: EuroQoL Questionnaire EQ-5D-5L, USA (English) Sample Version

Under each heading, please choose the ONE box that best describes your health TODAY.

CCI




CCI

Appendix M: COVID-19 Instructions

This appendix describes contingencies and accommodations for sites and subjects impacted by the COVID-19 pandemic. In response to the evolving circumstances of the pandemic, the Sponsor will provide ongoing guidance to Investigators on study conduct to ensure subject safety and maintain the scientific integrity of the study. Investigators must also maintain awareness of and respond to instructions and guidelines from their local regulatory authorities during the pandemic. These will be temporary measures and are applicable only during the pandemic, and as necessary to abide by local public health requirements. These measures will be repealed back to the measures described in the full study protocol as soon as the situation (governmental rules, benefit/risk assessment for the trial) allows.

Under the exceptional circumstances of the COVID-19 pandemic where randomized subjects are not able or willing to physically access the site clinic, the following accommodations may be permitted if allowed by local and other applicable regulations (Note: special accommodations are not permitted for screening assessments):

- Safety assessments should still be performed unless the Investigator and Sponsor agree that specific assessments may be missed as long as this occurs in accordance with all applicable local regulations. However, at a minimum, the Investigator or designee must regularly contact the subject (eg, by phone) to ascertain the subject's condition and occurrence of any symptom-based AEs per the relevant protocol-defined visit schedule. If available, results of any remote assessments performed by a non-study local oncologist or primary care physician must be sent to the Investigator for review and documentation. If components of the safety assessment cannot be collected or the timing of safety assessments needs to be adjusted, it may be possible to continue with study treatment but this will have to be discussed on a case-by-case basis with the Medical Monitor. Any remote laboratory assessments must be performed by laboratories accredited by the local jurisdiction.

- Tumor assessments may be performed at another radiology facility rather than at the study site (this option is not available in Germany). Such facilities should perform tumor assessments in accordance with the protocol, but alternative image acquisition protocols (eg, single post-contrast vs triple phase) may be accepted if the preferred modality is not available. The treatment modality (eg, CT scan or MRI) should be the same as that utilized since the start of study entry in order to avoid discrepancies in imaging interpretation. Imaging should be performed within or as close to the study visit window for scheduled imaging time points as possible. The study site must collect tumor images generated off site

in a timely fashion for review and documentation by the Investigator and submission to the BIRC.

- Alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations. Confirmation of drug receipt will be obtained by sites.

- Intravenous study treatment should generally only be administered at the study site, but circumstances may arise where the subject may receive infusions in another location under the supervision of the Investigator, with the approval of the Sponsor, and in accordance with all applicable regulations.

If logistical challenges in providing study treatment or performing study-related assessments result in temporary interruption of all study treatment for greater than 12 weeks, subjects are required to permanently discontinue study treatment unless permitted to continue by the Sponsor.

If it becomes necessary to employ any of the accommodations described in this appendix of COVID-19 Instructions, Investigators are to document each incident in source records as COVID-related. To comply with emerging regulatory guidance that such accommodations be reported and their impact on the study assessed, these will be collected by the Sponsor (or designee) as protocol-deviations. However, no corrective action will generally be expected if this appendix is followed.

Subjects are to be informed of changes to standard procedures resulting from effects of the COVID-19 pandemic, and if necessary subject consent is to be acquired. If additional consent is necessary during the course of the study but cannot be immediately obtained from the subject in writing, the Investigator is to describe to the subject the additional information requiring consent, obtain verbal consent from the subject, document such consent in the subject file, and follow up with written consent the next time a subject returns to the site. This does not apply to initial consent to enter the study; in this case, written consent is still required.

For subjects who develop COVID-19 while on study, the Investigator is to evaluate the overall risk-benefit ratio for the subject to determine whether holding study treatment(s) is in the best interest of the subject.

Any cases of confirmed or suspected COVID-19 infections should follow the general AE reporting requirements defined in the protocol. For any confirmed or suspected COVID-19 cases, the Investigator is responsible for assessing if the event should be reported as a SAE using

their clinical judgment. The investigator should further consider if the diagnosis meets the criteria of being a significant medical event.

When recording data missing, impacted, or related to COVID-19 in the electronic CRFs, the conventions below are to be employed. Also refer to updated CRF Completion Guidelines and site communication memos for additional instructions for how to document data missing or impacted by COVID-19.

Case Report Form	Instructions
Adverse Event CRF	• Record COVID-19 diagnoses as "COVID-19" • Record suspected cases as "suspected COVID-19" • If death is the outcome of such an event, the CTCAE grade should be assigned as '5'. See the CRF instructions for how to enter fatal events that started at a lower grade
End of Study Treatment CRFs	• Investigators are to use their best judgment to identify the primary reason for study treatment discontinuation. • If study treatment ended primarily due to a logistical issue associated with the COVID-19 pandemic and was unrelated to cancer progression or any AE: o Indicate "Other" as the reason for treatment discontinuation and describe the reason in the Specify field, including the term "COVID-19". For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions " • If study treatment ended primarily due to an AE caused by COVID-19 or suspected COVID-19: o Indicate "AE/SAE unrelated to progression of disease under study" o Record the AE on the Adverse Event CRF as described above with Action Taken = "Treatment Discontinued"
End of Radiographic Follow-Up CRF	• If radiographic assessments ended primarily due to a logistical issue or AE caused by COVID-19 or suspected COVID-19: o Indicate "Other" as the reason for discontinuation and describe the reason in the Specify field, including the term "COVID-19." For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions " or "Subject discontinued due to hospitalization for suspected COVID-19." In the latter example, also record the AE on the Adverse Event CRF as "suspected COVID-19"
Study Treatment CRFs	• If study treatment was held or delayed solely due to a logistical issue associated with the COVID-19 pandemic: o For oral study treatment CRFs: Indicate "Other" as the reason the dosing interval ended and describe the reason in the Specify field, including the term "COVID-19". o For IV dosing CRFs: Enter "Yes" for "Dose delayed from prior infusion" and "Reason for dose delay" should be

Case Report Form	Instructions
	entered as “Other” and describe the reason in the Specify field, including the term “COVID-19” (if/when ‘Specify’ field is available) For example – Other, Specify: “Subject unable to travel due to COVID-19 restrictions”