PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS CABOZANTINIB ALONE IN PATIENTS WITH INOPERABLE, LOCALLY ADVANCED, OR METASTATIC RENAL CELL CARCINOMA WHO EXPERIENCED RADIOGRAPHIC TUMOR PROGRESSION DURING OR AFTER IMMUNE CHECKPOINT INHIBITOR TREATMENT**
PROTOCOL NUMBER:	WO41994
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-000502-29
IND NUMBER:	119039
NCT NUMBER:	NCT04338269
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 3: See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
24-Mar-2021 00:12:03	[redacted]	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	24 June 2020
1	13 March 2020

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol WO41994 has been amended to primarily modify inclusion and exclusion criteria, and to update severe cutaneous adverse reactions (SCARs) from a potential risk to an identified risk associated with atezolizumab. Additional changes to the protocol, along with a rationale for each change, are summarized below. The synopsis has been updated to reflect changes made to the body of the protocol.

- Sections 1.4, 5.1, and Appendix 10 have been revised to include COVID−19-specific risk language to ensure the safety of study participants during the COVID-19 pandemic
- Sections 2.1.3 and 6.4.3, Exploratory Efficacy Objectives, now include clarification of timepoints and instruments for patient-reported outcomes (PROs)
- Section 3.1, Description of the Study, has been revised:
  - To clarify sites must continue to provide images until the Independent Review Facility (IRF) determines disease progression
  - To align the key eligibility criteria changes in the study schema with inclusion and exclusion criteria
- Section 4.1.1, Inclusion Criteria, has been revised:
  - To allow inclusion of patients with the chromophobe subtype of non−clear-cell renal cell carcinoma (non-ccRCC) if there is sarcomatoid differentiation because studies have shown improved survival for patients with sarcomatoid differentiation after treatment with immune checkpoint inhibitors (ICIs)
  - Patients must have been treated with ICIs for at least 2 cycles prior to study enrollment to reflect a biologically-relevant minimum exposure
  - To allow inclusion of patients who have received ICIs in the adjuvant setting, provided they progressed during or within 6 months after the last dose of adjuvant ICI. Phase III renal cell carcinoma (RCC) trials are ongoing in the adjuvant setting with ICIs. Thus, ICIs are becoming the standard of care in the adjuvant setting for patients with RCC. Progression during or within 6 months after the last dose of ICI in the adjuvant setting is a commonly applied inclusion criterion in oncology clinical trials.
  - Patients must have recovered to baseline or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5 Grade ≤ 1 from toxicities related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable in the opinion of the investigator to ensure patient safety. Grade 2 alopecia is allowed for study participation. Exception: Patients who have received systemic corticosteroids for a prior immune-related adverse events for >30 days consecutively prior to initiation of study treatment are excluded to ensure patient safety.

- Section 4.1.2, Exclusion Criteria, has been revised:
  - The time window has been shortened for “treatment with anti-cancer therapy prior to initiation of study treatment” from “within 28 days” to “within 14 days.” The rationale is to “shorten” the 28-day washout period requirement considering that many RCC-targeted agents have a short half-life.
  - Patients who have received a mammalian target of rapamycin (mTOR) inhibitor in any setting are excluded from the study to reduce heterogeneity of the study population. Previously only patients who received an mTOR inhibitor in the advanced or metastatic settings were excluded.
  - The time window for excluding patients with prior ischemic events or significant cardiovascular disease risks has been clarified
  - Additional standard language has been added to exclusion criteria. This language serves to address cabozantinib risks, including hemorrhage, perforation, and fistulas.
- Section 4.3.2.2, Cabozantinib, has been revised so that the requirement for the 1-hour wait time in the clinic after the first dose of cabozantinib has been removed because it was deemed clinically unnecessary
- Section 4.5.10.3, Research Biosample Repository (RBR), and Appendix 2 have been updated to clarify that RBR sample collection should occur preferably predose on Day 1 of Cycle 1 but may also be collected anytime thereafter
- Section 5.1.1 and Appendix 10 have been updated because SCARs have been upgraded to an identified risk associated with atezolizumab
- Section 5.2.3, Adverse Events of Special Interest, has been updated to reflect the most up-to-date listing of these events for immediate reporting purposes
- Section 5.4.1, Emergency Medical Contacts, has been updated. The Medical Monitor has been changed.
- Section 9.6, Dissemination of Data and Protection of Trade Secrets, has been updated to correct the name of a Roche policy on data sharing
- Appendix 1 and Appendix 2 have been updated:
  - The urine protein-to-creatinine ratio (UPCR) sampling schedule has been clarified (Appendix 1)
  - A urine biomarker sample is now required for specific visits (Appendix 1 and Appendix 2)
- Appendix 7 has been updated to add language clarifying that hemophagocytic lymphohistiocytosis and macrophage activation syndrome are considered potential risks for atezolizumab

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

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PROTOCOL NUMBER:	WO41994
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-000502-29160
IND NUMBER:	119039
NCT NUMBER:	NCT04338269
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS CABOZANTINIB ALONE IN PATIENTS WITH INOPERABLE, LOCALLY ADVANCED, OR METASTATIC RENAL CELL CARCINOMA WHO EXPERIENCED RADIOGRAPHIC TUMOR PROGRESSION DURING OR AFTER IMMUNE CHECKPOINT INHIBITOR TREATMENT**
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VERSION NUMBER:	3
EUDRACT NUMBER:	2020-000502-29160
IND NUMBER:	119039
NCT NUMBER:	NCT04338269
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Renal cell carcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab when given in combination with cabozantinib compared with cabozantinib alone in patients with advanced clear-cell or non–clear-cell renal cell carcinoma (RCC; papillary*, chromophobe or* unclassified only) who experienced radiographic tumor progression during or after immune checkpoint inhibitor (ICI) treatment in the *adjuvant and/or locally advanced/*metastatic setting. Patients with RCC with sarcomatoid features are also allowed into this study. *Patients with the chromophobe subtype of non–clear-cell RCC must have sarcomatoid differentiation.* Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab in combination with cabozantinib or cabozantinib monotherapy).

Efficacy Objectives

Response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Objective response at a single timepoint will be determined by the investigator and Independent Review Facility (IRF) according to RECIST v1.1. Objective response rate (ORR) per modified RECIST for immune-based therapeutics (iRECIST) v1.1 may be calculated programmatically by the Sponsor on the basis of investigator assessments of individual lesions at each specified timepoint.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone in the intent-to-treat (ITT) population based on the following endpoints:

- Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1, as assessed by an IRF (e.g., IRF-PFS) or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from randomization to death from any cause

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- PFS assessed by the investigators (investigator-assessed PFS), defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1 or death from any cause (whichever occurs first)
- Investigator- and IRF-assessed ORR (investigator-assessed ORR and IRF-assessed ORR), defined as the proportion of patients with a complete response or partial response on two consecutive occasions at least 4 weeks apart according to RECIST v1.1
- Investigator- and IRF-assessed duration of response (DOR; investigator-assessed-DOR and IRF-DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) according to RECIST v1.1

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- PFS, OS, and ORR in subgroups, defined by demographic and baseline characteristics (e.g., PD-L1 status, prior vascular endothelial growth factor receptor [VEGFR]-tyrosine kinase inhibitor [TKI] use, most recent ICI therapy [*adjuvant vs.* first-line vs. second-line], tumor histology, or International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] risk group)
- Time to response
- Time to *confirmed* deterioration of disease-related symptoms, defined as the time from randomization date to the date of a patient's first ≥4-point score decrease from baseline *on* the Functional Assessment of Cancer Therapy–Kidney Symptom Index 19 (FKSI-19) Disease-Related Symptom-Physical (DRS-P) scale *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last patient-reported outcome (PRO) assessment*
- Change from baseline in patient-reported disease-related symptoms by visit, measured with use of the FKSI-19 DRS-P scale
- Time to *confirmed* deterioration of physical functioning, defined as the time from randomization date to the date of a patient's first ≥10-point score decrease from baseline *on* the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30) physical functioning scale *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*
- Time to *confirmed* deterioration of global health status*/quality of life (GHS/QoL)*, defined as the time from randomization date to the date of a patient's first ≥10-point score decrease from baseline *on* the EORTC QLQ-C30 *GHS/QoL* scale *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*

- Change from baseline in patient-reported physical functioning and global health status by visit, measured with use of the EORTC QLQ-C30 physical functioning and GHS/QoL scales
- Descriptive summary statistics by visit for the remaining FKSI-19 and EORTC QLQ-C30 scales
- Cumulative distribution function curves of score change from baseline to Month 6 for each key scale (FKSI-19 DRS-P, EORTC QLQ-C30 physical function, EORTC QLQ-C30 GHS/QoL)

Safety Objective

The safety objective for this study is to evaluate the safety of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the overall side-effect burden of atezolizumab in combination with cabozantinib compared with cabozantinib alone from the patient's perspective, on the basis of the following endpoint:

- Patient-reported overall bother with treatment side effects during study treatment, measured with use of the FKSI-19 GP5 item

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab and cabozantinib administered in combination on the basis of the following endpoints:

- Atezolizumab concentrations at specified timepoints
- Cabozantinib concentrations at specified timepoints

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and demographics, efficacy, safety, or PK endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to atezolizumab in combination with cabozantinib or cabozantinib alone (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab in combination with cabozantinib or cabozantinib alone, can provide evidence of atezolizumab in combination with cabozantinib or cabozantinib alone efficacy (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood, tumor tissue$, and\ urine$ and efficacy, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with atezolizumab in combination with cabozantinib compared with cabozantinib alone to inform economic modeling on the basis of the following endpoint:

- Change from baseline in the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and visual analog scale (VAS) scores by visit

Study Design

Description of Study

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab given in combination with cabozantinib versus cabozantinib alone in patients with inoperable, locally advanced, or metastatic RCC who experienced radiographic tumor progression during or after ICI treatment in the *adjuvant and/or locally advanced/*metastatic setting. The study will enroll approximately 500 patients at approximately 140–180 sites globally.

Key inclusion criteria include:

- Male and female patients aged ≥ 18 years with Karnofsky Performance Status (KPS) score ≥ 70 who have histologically-confirmed locally advanced or metastatic clear-cell or non–clear-cell RCC (papillary*, chromophobe, or* unclassified only)

  Sarcomatoid features are allowed. Patients with the chromophobe subtype of non–clear-cell RCC must have sarcomatoid differentiation.

  Other subtypes of non–clear-cell RCC (e.g., collecting duct carcinoma, renal medullary carcinoma) are not eligible.
- *Patients who have experienced radiographic tumor progression during or following ICI treatment for locally advanced or metastatic RCC either in first-line or second-line treatment. Patients who experienced radiographic tumor progression during or within 6 months after last dose of adjuvant ICI are also eligible.*

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log.

Patients will be randomized in a 1:1 ratio to one of the following two treatments arms:

- Experimental arm: Atezolizumab 1200 mg IV infusions every 3 weeks (Q3W) on Day 1 of each 21-day cycle plus cabozantinib 60-mg oral tablets taken once a day (QD; 1 cycle = 21 days)
- Control arm: Cabozantinib 60-mg oral tablets taken QD (1 cycle = 21 days)

Randomization will be stratified by:

- IMDC risk groups (*favorable*, intermediate or *poor* risk; 0, 1–2, or ≥ 3), which comprises the following six risk factors: time from diagnosis to systemic therapy, KPS, hemoglobin, corrected calcium, neutrophil and platelet count
- Most recent ICI therapy (*adjuvant vs.* first-line vs. second-line)
- Histology: dominant clear-cell without sarcomatoid versus dominant non–clear-cell (papillary or unclassified only) without sarcomatoid versus any sarcomatoid component (clear-cell or non–clear-cell)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle and cabozantinib will be taken orally at a starting dose of 60 mg/day on Days 1–21 of each 21-day cycle. Patients randomized to the atezolizumab and cabozantinib arm who transiently withhold or permanently discontinue either atezolizumab or cabozantinib may continue on single-agent therapy until disease progression (i.e., patients being withheld from

cabozantinib transiently for adverse effects may continue atezolizumab monotherapy and vice versa). Guidelines for dosage modification, treatment interruption or discontinuation.

Patients will receive atezolizumab and/or cabozantinib until disease progression per RECIST v1.1, unacceptable toxicity, or symptomatic deterioration attributed to disease progression (e.g., pain secondary to disease or unmanageable ascites) as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline, every 9 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter. Tumor assessments will continue until disease progression as assessed by the investigator per RECIST v1.1 or, for patients who continue study treatment after radiographic disease progression, loss of clinical benefit as determined by the investigator. In the absence of disease progression, tumor assessments should continue regardless of whether treatment has been discontinued (e.g., for toxicity) or whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. Following treatment discontinuation (even in the absence of disease progression per RECIST v1.1.), patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first. The following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, date of first dose of agent, date of final dose of agent (or if ongoing), patient's best response, and date of disease progression.

Sites must continue to provide images until the IRF determines disease progression. However, treatment decisions will be made based on investigator assessment of disease progression. Independent Review Facility procedures will be detailed in an IRF Charter.

Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudo progression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab and/or cabozantinib will be permitted to continue treatment, until loss of clinical benefit, if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in KPS that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom other treatment options/standard therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression

Tumor tissue will also be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 (within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner. These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab and/or cabozantinib.

Number of Patients

Approximately 500 patients will be enrolled in this study at approximately 140–180 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically-confirmed locally advanced or metastatic clear-cell or non–clear-cell (papillary, *chromophobe,* unclassified only) RCC
  - Other subtypes of non–clear-cell RCC (e.g., collecting duct carcinoma, renal medullary carcinoma) are not eligible.
  - R*CC* with sarcomatoid features is allowed. *Patients with the chromophobe subtype of non-clear-cell RCC must have sarcomatoid differentiation.*
- Radiographic disease progression *to prior ICI therapy for* RCC
  - *ICI for metastatic disease: Radiographic disease progression during or following ICI treatment for locally advanced or metastatic RCC either in first- or second-line treatment*
  - *ICI for adjuvant therapy: Patients who experienced radiographic tumor progression during or within 6 months after last dose of adjuvant ICI are also eligible*
  - *Examples of ICI regimens include one* ICI *regimen* in first-line treatment (e.g., nivolumab plus ipilimumab, pembrolizumab plus axitinib, axitinib plus avelumab)*, or* second-line treatment (e.g., TKI as first-line treatment and ICI as second-line treatment)
  - ICI is defined by anti–PD-L1 or anti–PD1 antibody, including atezolizumab, avelumab, pembrolizumab, *durvalumab,* or nivolumab. Ipilimumab monotherapy is not considered an anti–PD-L1 or anti–PD1 therapy.
  - *Patients must have received at least 2 cycles of ICI treatment*
  - *ICI must have been used in the immediate preceding line of therapy* (patients with an intervening treatment between ICI and study screening are excluded)
  - *Adjuvant treatment with VEGFR-TKIs, except cabozantinib, is allowed*
- Measurable disease per RECIST v1.1
- Evaluable IMDC risk scores
- Representative pretreatment tumor specimen(s), for exploratory biomarker research
  - Archival tumor specimen (e.g., at diagnosis, surgery, or prior to initiation of previous line of therapy)
  - Pretreatment tumor tissue from fresh biopsy at screening, if clinically feasible. Biopsies collected via minor surgery must be performed at least 10 days prior to Day 1 of Cycle 1 and must be completely healed before first dose.

    Availability of tissue sample(s) must be confirmed before randomization.
    Tissue samples must be submitted before or within 4 weeks of randomization.
    Both archival and fresh samples are preferred, if feasible.
- KPS score of ≥70
- *Recovery to baseline or Grade ≤1 NCI CTCAE v5.0 from toxicities related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable in the opinion of the investigator*
  - *Grade 2 alopecia is allowed for study participation*
  - *Exception: Patients who have received systemic corticosteroids for a prior immune-related adverse event for >30 days consecutively prior to initiation of study treatment are not eligible. Additional criteria on steroid use for prior immune-related adverse events is described in the exclusion criteria.*

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500 cells/μL) without granulocyte colony-stimulating factor support within 14 days prior to Day 1 of Cycle 1
  - Lymphocyte count $\geq 0.3 \times 10^9$/L (300/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion within 14 days prior to Day 1 of Cycle 1
  - WBC counts ≥ 2500 cells/μL
  - Hemoglobin ≥ 90 g/L (9 g/dL) (without transfusion within 14 days prior to Day 1 of Cycle 1)
  - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

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

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: bilirubin $\leq 3 \times$ ULN
  - Creatinine clearance $\geq$ 40 mL/min (calculated with use of the Cockcroft-Gault formula, or based on 24-hour urine collection)
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
  - Proteinuria, as demonstrated by urine protein-to-creatinine ratio ≤ 1 mg/mg (≤ 113.2 mg/mmol)
- Negative HIV test at screening
- Negative hepatitis B testing at screening:
  - Negative hepatitis B surface antigen (HBsAg) test at screening
  - Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 4 months after the final dose of cabozantinib and for 5 months after the final dose of atezolizumab. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 months after the final dose of cabozantinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Females of childbearing potential who are partners of male patients should also use contraceptive methods with a failure rate of <1% per year during their male partner's therapy and for at least 4 months after completing therapy. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment with anti-cancer therapy within *14* days prior to initiation of study treatment
- Patients received cabozantinib at any time prior to screening
- Patients who received more than one ICI treatment *in the locally advanced or metastatic setting* (e.g., pembrolizumab and axitinib as first-line treatment and nivolumab as second-line treatment)
- Patients who received more than two prior lines of therapy in the locally advanced or metastatic setting
- Patients who have received a mTOR inhibitor in *any* setting
- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
  - No evidence of significant vasogenic edema
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

- There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- History of leptomeningeal disease
- Uncontrolled tumor-related pain

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Moderate to severe hepatic impairment (Child-Pugh B or C)
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

  Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- History of malignancy other than renal carcinoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Radiotherapy for RCC within 14 days prior to Day 1 of Cycle 1

  Patients who are receiving single-fraction radiotherapy given for the indication of pain control are eligible.
- Active tuberculosis
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Minor surgeries (e.g., tumor biopsy, placement of vascular access device) should be performed at least 10 days prior to initiation of study treatment. Patients must have complete wound healing from major surgery or minor surgery before randomization. Patients with clinically relevant ongoing complications from prior surgery are not eligible.
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after final dose of atezolizumab and 4 months after final dose of cabozantinib

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose systemic immunosuppressant medication (e.g., $\leq$10 mg/day oral prednisone or equivalent) or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Current treatment with anti-viral therapy for HBV or HCV
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, vasculitis, or glomerulonephritis, or multiple sclerosis, with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided <u>all</u> of following conditions are met:
  - Rash must cover $<$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
- *Pharmacologically uncompensated, symptomatic hypothyroidism*
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- *Malabsorption syndrome*
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

- Uncontrolled hypertension defined as sustained blood pressure > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment
- *Tumors invading the gastrointestinal (GI) tract, active peptic ulcer disease, acute pancreatitis, acute obstruction of the pancreatic or biliary duct, appendicitis, cholangitis, cholecystitis, diverticulitis, gastric outlet obstruction, or inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)*
- Stroke (including transient ischemic attack), myocardial infarction, or other symptomatic ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT], pulmonary embolism [PE]) within 6 months before *randomization*

  Upon Sponsor approval, subjects with a diagnosis of incidental PE or DVT within 6 months are allowed if asymptomatic *and stable at screening* treated with low–molecular-weight heparins (LMWHs) or *the direct factor Xa inhibitors* rivaroxaban, edoxaban, or apixaban for at least 1 week before first dose.
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, *unstable arrhythmia, or unstable angina*) within 3 months prior to initiation of study treatment
- History of clinically significant ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History of congenital QT syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction that is considered as clinically significant by investigator
- QT interval corrected with use of Fridericia's formula (QTcF) > 480 ms per ECG within 14 days before randomization

  Note: If a single ECG shows a QTcF with an absolute value > 480 ms, 2 additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of the 3 consecutive results for QTcF must be ≤ 480 ms for the patient to be eligible.
- Significant vascular disease (e.g., aortic aneurysm *or arterial dissection* requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy
- Abdominal or tracheoesophageal fistula*, bowel obstruction,* or GI perforation*, or intra-abdominal abscess* within 6 months *before initiation of study treatment*

  Complete healing of an intra-abdominal abscess must be confirmed before initiation of study treatment.
- Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel)

  The following are allowed anticoagulants:

  Prophylactic use of low-dose aspirin for cardio protection (per local applicable guidelines) and low-dose LMWHs.

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in patients without known brain metastases who are on a stable dose of the anti-coagulant for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
- Clinical signs or symptoms of GI obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding

- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- *Known cavitating pulmonary lesion(s) or known endobronchial disease manifestations*
- *Lesions invading major pulmonary blood vessels*
- *Clinically significant hematuria, hematemesis, hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, coagulopathy, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before initiation of study treatment*
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Prior history of hypertensive crisis or hypertensive encephalopathy
- *Requirement for hemodialysis or peritoneal dialysis*
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known allergy or hypersensitivity to any component of the cabozantinib formulation
- Patients who are not able to swallow a tablet

End of Study

The end of this study is defined as the date when the required numbers of events for the final analysis of OS in the ITT population has occurred.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 55 months.

Investigational Medicinal Products

The investigational medicinal products for this study are atezolizumab and cabozantinib.

Test Products (Investigational Drugs)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W.

Cabozantinib will be administered orally QD at a dose of 60 mg (three 20-mg tablets).

Comparator

The comparator of this study is cabozantinib 60 mg (three 20-mg tablets) administered orally QD.

Statistical Methods

Efficacy Analyses

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

Multiple Primary Efficacy Endpoints

The multiple primary efficacy endpoints are IRF-assessed PFS per RECIST v1.1 and OS.

Progression-free survival is defined as the time from randomization to disease progression, as determined by the IRF per RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date.

Overall survival is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization.

The following analyses will be performed for both PFS and OS endpoints described above. Progression-free survival and OS will be compared between treatment arms with use of the

stratified log-rank test at the 2-sided level of significance. The hazard ratio (HR) with a 95% CI will be estimated with use of a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. The randomization stratification factors are most recent ICI therapy (*adjuvant vs.* first-line vs. second-line), histology (dominant clear-cell without sarcomatoid vs. dominant non–clear-cell [papillary or unclassified only] without sarcomatoid vs. any sarcomatoid component [clear-cell or non–clear-cell]), and the IMDC score (0, 1–2, ≥ 3). If at least 1 stratum has less than 10 events at the time of analysis, the stratification factor that contains the level with the smallest number of patients will be removed from the stratified analyses. The final set of stratification factors used for the multiple primary endpoints will be applied to all other endpoints where stratified analyses are planned. The stratification factors will be obtained from the interactive voice or Web-based response system (IxRS) at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS and OS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

Determination of Sample Size

Approximately 500 patients are planned for enrollment globally over 20 months. The sample size calculation is determined based on the below considerations.

Type I Error Control

The type I error (α) for the entire study is 0.05 (2-sided). There are multiple primary efficacy endpoints for this study: PFS by IRF assessment per RECIST v1.1 and OS in the ITT population. To control the overall type I error rate at $\alpha = 0.05$ while accounting for 2 primary endpoints, α is split between PFS ($\alpha = 0.02$) and OS ($\alpha = 0.03$). The type I error can be recycled if PFS results in the ITT population are statistically significant at $\alpha = 0.02$, then $\alpha = 0.02$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$. The study will be considered as a positive study if statistical significance is achieved in favor of the experimental arm for either of the multiple primary endpoints, since the type I error (α) for the entire study is controlled at 0.05.

Primary Endpoint: Progression-Free Survival by Independent Review Facility Assessment per RECIST v1.1 in the Intent-to-Treat Population

The analysis of the primary endpoint of PFS by IRF assessment per RECIST v1.1 will take place when approximately 325 IRF-assessed PFS events have occurred in the ITT population (65% events patient rate) based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.02$ (2-sided)
- Approximately 90% power
- Median PFS for the cabozantinib arm of 8.0 months and estimated median PFS in the atezolizumab and cabozantinib arm of 11.9 months (corresponding to HR of 0.67)
- 5% annual loss to follow-up for PFS
- No interim analysis

On the basis of these assumptions, it is projected that an observed HR of 0.77 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.77 will be the minimum detectable difference [MDD] for the analysis; this corresponds to an improvement of 2.4 months in median PFS from 8.0 months in the cabozantinib arm to 10.4 months in the atezolizumab and cabozantinib arm).

Primary Endpoint: Overall Survival in the Intent-to-Treat Population

The final analysis of the primary endpoint of OS will take place when approximately 325 OS events have occurred in the ITT population (65% events patient rate) based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.03$ (2-sided)
- Approximately 85% power

- Median OS in the cabozantinib arm of 22 months and estimated median OS in the atezolizumab and cabozantinib arm of 31.4 months (an increase of 9.4 months, corresponding to an HR of 0.70)
- 1% annual loss to follow-up for OS
- Two interim OS analyses

At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.78 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the MDD at the analysis; this corresponds to an improvement of 6.2 months in median OS, from 22 months in the control arm to 28.2 months in the atezolizumab and cabozantinib arm).

Sample Size

With the above assumptions on PFS and OS, the sample size is determined at 500 patients, where the PFS and OS final analysis will be conducted when 325 events occur (65% events patient rate), respectively. The 500 patients are planned for enrollment globally over 20 months.

Interim Analyses

Primary Endpoint of Progression-Free Survival

There is no planned interim analysis of the primary endpoint of PFS.

Primary Endpoint of Overall Survival

A total of three analyses of OS will be performed, including two interim analyses and one final analysis. The boundary for statistical significance at each OS analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming (OBF) function to maintain the overall type I error rate at either 0.03 or 0.05 level, depending on whether primary endpoint of PFS is significant at 0.02 level. The OS endpoint will be considered positive in the ITT population if statistical significance is achieved in favor of the experimental arm for any of the two OS interim analyses or the final analysis.

The first interim analysis of OS will be performed at the time of the PFS primary analysis. A total of 175 OS events are expected at the first interim analysis of OS, which corresponds to 53% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p < 0.0019$. If there are significantly fewer (< 160) OS events than the expected 175 OS events, then the first interim analysis will be delayed until 175 OS events occur. An administrative α of 0.000001 (negligible impact on overall type I error rate) will be spent on the OS hypothesis at the time of the planned PFS.

The second interim analysis of OS will be performed when approximately 260 deaths have occurred, which corresponds to approximately 80% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p < 0.0125$.

The final analysis of OS will be performed when 325 deaths (65% of 500 patients in the ITT population) have occurred. Statistical significance will be declared if $p < 0.0259$ when exactly 325 deaths have occurred at the time of the final OS analysis.

The actual OBF boundary will be calculated at time of analysis based on actual number of events observed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
aRCC	advanced renal cell carcinoma
AUC	area under the concentration-time curve
BP	blood pressure
ccRCC	clear-cell renal cell carcinoma
COPD	chronic obstructive pulmonary disease
CR	complete response
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography (scan)
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
DRS-P	Disease-Related Symptom-Physical
DVT	deep venous thrombosis
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
FKSI-19	Functional Assessment of Cancer Therapy–Kidney Symptom Index 19
GI	gastrointestinal
GHS/QoL	global health status/quality of life
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
IL	interleukin
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
iRECIST	modified RECIST for immune-based therapeutics
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intention-to-treat
IxRS	interactive voice or Web-based response system
KPS	Karnofsky Performance Status
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
MDD	minimum detectable difference
MDSC	myeloid-derived suppressor cell
mOS	median overall survival
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
non–ccRCC	non–clear-cell renal cell carcinoma
NSAID	nonsteroidal anti-inflammatory inhibitor
NSCLC	non–small-cell lung cancer
OBF	O'Brien-Fleming
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PE	pulmonary embolism
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	proton pump inhibitor
PPE	palmar-plantar erythrodysesthesia

Abbreviation	Definition
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
QD	once a day
QLQ-C30	Quality of Life–Core 30 Questionnaire
QTc	corrected QT interval
QTcF	QT interval corrected with use of Fridericia's formula
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
USPI	U.S. Package Insert
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WES	whole-exome sequencing
WGS	whole-genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) was diagnosed in more than 400,000 people and was associated with approximately 175,000 deaths worldwide in 2018. Renal cell carcinoma is the 9th most common cancer occurring in men, and the 14th most common cancer in women (GLOBACON 2018). The incidence of RCC is predominant in men with a peak age of 60–70 years (Capitanio and Montorsi 2016). Renal cell carcinoma comprises a heterogeneous group of cancers with clear-cell renal cell carcinoma (ccRCC) being the most common histologic subtype (75%), followed by non–clear-cell renal cell carcinoma (non–ccRCC) subtypes of papillary (15%), and chromophobe and oncocytoma (5% each; Motzer et al. 1996). With the exception oncocytoma, a sarcomatoid component can develop in each of these subtypes.

While the majority of patients will present with localized disease, approximately 30% of those treated with curative intent will develop distant disease, and approximately 20%–25% of patients present with metastatic disease at initial diagnosis (Dabestani et al. 2016). The models to predict survival such as the Memorial Sloan Kettering Cancer Center (MSKCC; Motzer et al. 2004) risk stratification model and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC; Heng et al. 2009) risk score have been developed. These models are used as a stratification factor for the clinical trials with use of immune checkpoint inhibitors (ICIs). The IMDC risk category is also validated for the patients receiving second-line targeted therapy (Ko et al. 2015).

1.2 FIRST-LINE TREATMENT FOR RENAL CELL CARCINOMA

The tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor (VEGF), sunitinib, was the standard of care for treatment-naive patients with RCC for many years because of the data showing superior efficacy over conventional cytokines (Table 1). However, the first-line treatment landscape has evolved significantly in recent years with the upfront use of ICIs and the results suggest that the upfront use of ICIs improves overall survival (OS) when compared with sunitinib (Table 1).

Table 1 First-Line Therapy Results for Advanced Renal Cell Carcinoma

Agent and Population	Comparison	PFS (months)	HR (95% CI)	OS (months)	HR (95% CI)
Nivo + Ipi (int–poor risk) [a]	Sunitinib	11.6 vs. 8.4	0.82 0.64–1.05	NR vs. 26.0	0.63 0.44–0.89
Atezo + Bev (PD-L1+) [b]	Sunitinib	11.2 vs. 7.7	0.83 0.70–0.97	N/A	N/A
Ave + Axi [c]	Sunitinib	13.8 vs. 8.4	0.69 0.56–0.84	NR vs. NR	0.78 0.55–1.08
Pembro + Axi [d]	Sunitinib	15.1 vs. 11.1	0.69 0.57–0.84	NR vs. NR	0.53 0.38–0.74
Sunitinib [e]	IFN-α	11.0 vs. 5	0.42 0.32–0.54	24.5 vs. 20.4	0.82 0.67–1.00
Bev + IFN-α [f]	IFN-α	10.2 vs. 5.4	0.63 0.52–0.75	23.0 vs. 21.0	0.96 0.73–1.04
Pazopanib [g]	Placebo	9.2 vs. 4.2	0.46 0.34–0.62	22.9 vs. 20.5	0.91 0.71–1.16
Temsirolimus [h] (poor risk)	IFN-α	5.6 vs. 3.2	0.74 0.60–0.91	10.9 vs. 7.3	0.78 0.63–0.97
Cabozantinib (int–poor risk)	Sunitinib	8.2 vs. 5.6 [i]	0.66 0.46–0.95	26.6 vs. 21.2 [j]	0.80 0.53–1.21
Cabo + Nivo [k]	*Sunitinib*	*16.6 vs. 8.3*	*0.51 0.41–0.64*	*NR vs. NR*	*0.60 0.40–0.89* [m]
Lenv + Pembro [l]	*Sunitinib*	*23.9 vs 9.2*	*0.39 0.32–0.49*	*NR vs NR*	*0.66 0.49–0.88*
Lenv + Eve [l]	*Sunitinib*	*14.7 vs 9.2*	*0.65 0.53–0.80*	*NR vs NR*	*1.15 0.88–1.50*

Atezo = atezolizumab; Ave = avelumab; Axi = axitinib; Bev = bevacizumab; *Cabo = cabozantinib; Eve = everolimus;* HR = hazard ratio; int–poor = intermediate–poor; Ipi = ipilimumab; *Lenv = lenvatinib;* N/A = not available; Nivo = nivolumab; NR = not reached; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival.

[a] Source: Motzer et al. 2018a.

[b] Source: Rini et al. 2019a.

[c] Source: Motzer et al. 2019b.

[d] Source: Rini et al. 2019b.

[e] Source: Motzer et al. 2007.

[f] Source: Escudier et al. 2007.

[g] Source: Sternberg et al. 2010.

[h] Source: Hudes et al. 2007.

[i] Source: Choueiri et al. 2017a.

[j] Source: Choueiri et al. 2018.

[k] *Source: Cabometyx™ U.S. Package Insert.*

[l] *Source: Motzer et al. 2021.*

[m] *Hazard ratio (98.89% CI).*

1.3 SECOND-LINE AND THIRD-LINE TREATMENT

There are several options available for patients with RCC who received prior systemic therapy (Table 2). Everolimus and sorafenib have shown a progression-free survival (PFS) benefit for patients previously treated with anti-angiogenic agents over placebo (Escudier et al. 2009; Motzer et al. 2010). Later, axitinib demonstrated a longer PFS against sorafenib for those previously treated with anti-angiogenic agents or interleukin (IL)-2 (Rini et al. 2011). Similarly, in a Phase II study, lenvatinib plus everolimus demonstrated PFS benefit in comparison with everolimus alone in patients with ccRCC previously treated with anti–VEGF-targeted therapy and progressed in or within 9 months of stopping the previous treatment. However, the numerical increase seen in OS was not statistically significant. Cabozantinib demonstrated a longer PFS and OS over everolimus in patients previously treated with VEGF receptor (VEGFR)-TKI (Choueiri et al. 2015). Nivolumab demonstrated an OS benefit for those patients previously treated with anti-angiogenic therapy in ccRCC regardless of PD-L1 status, prior therapy or MSKCC risk group (Motzer et al. 2015a).

With the shift to immunotherapy combinations increasingly being used in first-line therapy, there have been no completed Phase III studies in the post-immunotherapy setting for RCC. In the pre-immunotherapy era, a report suggested that only 55 patients received third-line therapy out of 257 patients who received second-line therapy, and treatments vary, including sorafenib, everolimus, axitinib, temsirolimus, and bevacizumab (Maroun et al. 2018). Another report revealed that third-line therapy was given to 21% of patients who received first-line therapy. Everolimus was the most prevalent therapy, and other treatments included in the third-line therapy were sunitinib, sorafenib, pazopanib, temsirolimus, and axitinib. Overall survival for the patients who received third-line therapy was 12.4 months and PFS was 3.9 months (Wells et al. 2017).

Table 2 Second-Line Therapy Results for Advanced Renal Cell Carcinoma

Agent and Population	Comparison	PFS (months)	HR (95% CI)	OS (months)	HR (95% CI)
Nivo [a]	Everolimus	4.6 vs. 4.4	0.88 0.75–1.03	25.0 vs. 19.6	0.73 0.57–0.93
Everolimus [b]	Placebo	4.9 vs. 1.9	0.33 0.25–0.43	14.8 vs. 14.4	0.87 0.65–1.17
Sorafenib [c]	Placebo	5.5 vs. 2.8	0.44 0.35–0.55	17.8 vs. 15.2	0.88 0.74–1.04
Axitinib [d]	Sorafenib	6.7 vs. 4.7	0.67 0.54–0.81	20.1 vs. 19.2	0.97 0.80–1.17
Lenva + Everolimus [e]	Everolimus	14.6 vs. 5.5	0.44 0.24–0.68	25.5 vs. 18.4	0.55 0.30–1.01
Cabozantinib [f]	Everolimus	7.4 vs 3.8	0.58 0.45–0.75	21.4 vs. 16.5	0.66 0.53–0.83 [a]

HR = hazard ratio; Lenva = Lenvatinib; NA = not assessed; Nivo = nivolumab; OS = overall survival; PFS = progression-free survival.

[a] Source: Motzer et al. 2015a.

[b] Source: Motzer et al. 2010.

[c] Source: Escudier et al. 2009.

[d] Source: Rini et al. 2011.

[e] Source: Motzer et al. 2015b.

[f] Source: Cabometyx™ U.S. Package Insert.

1.4 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single-agent therapy, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy and is approved for the treatment of urothelial carcinoma, non–small-cell lung cancer (NSCLC), small-cell lung cancer, and triple-negative breast cancer.

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

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

1.4.1 Efficacy in Metastatic Renal Cell Carcinoma

Atezolizumab monotherapy (1200 mg, every 3 weeks [Q3W]) with or without bevacizumab (15 mg/kg, Q3W) was compared with sunitinib for treatment-naive metastatic RCC in the Phase II Study WO29074 (IMmotion150). In the intent-to-treat (ITT) population, PFS hazard ratios (HRs) for atezolizumab in combination with bevacizumab or atezolizumab monotherapy versus sunitinib were 1.0 (95% CI: 0.69–1.45) and 1.19 (95% CI: 0.82–1.71), respectively; PD-L1+ PFS HRs were 0.64 (95% CI: 0.38–1.08) and 1.03 (95% CI: 0.63–1.67), respectively. The objective response rates (ORRs) in the ITT population were 32% (7% complete response [CR],

25% partial response [PR]), 25% (11% CR, 14% PR), and 29% (5% CR, 24% PR) with atezolizumab in combination with bevacizumab, atezolizumab monotherapy, and sunitinib, respectively. In PD-L1+ patients, the ORRs were 46% (12% CR, 34% PR), 28% (15% CR, 13% PR), and 27% (7% CR, 20% PR) with atezolizumab in combination with bevacizumab, atezolizumab monotherapy, and sunitinib, respectively (McDermott et al. 2018). This trial allowed crossover to atezolizumab and bevacizumab treatment after treatment failure with sunitinib or atezolizumab monotherapy. The ORRs in atezolizumab plus bevacizumab for patients previously treated with sunitinib or atezolizumab monotherapy was 28% and 24%, respectively. The PFS in atezolizumab plus bevacizumab for patients previously treated with sunitinib or atezolizumab monotherapy was 8.3 months and 12.6 months, respectively (Atkins et al. 2017). These results appear to suggest potential use of atezolizumab combination therapy after atezolizumab treatment failure, although the results are preliminary.

The Phase III Study WO29637 (IMmotion151) was designed to demonstrate the superiority of atezolizumab in combination with bevacizumab compared with sunitinib for advanced, treatment-naive patients with ccRCC or RCC with sarcomatoid component (Rini et al. 2019a). The study met its co-primary endpoint of investigator-assessed PFS in PD-L1+ patients, but OS data was immature at the time of analysis (median PFS for atezolizumab plus bevacizumab vs. sunitinib: 11.2 months vs. 7.7 months; HR=0.74; p=0.0217; median OS HR=0.93). In addition, PFS results with an independent radiology committee showed a HR=0.93 (95% CI: 0.72–1.21) in the PD-L1+ population.

Atezolizumab administered in combination with bevacizumab was also assessed in patients with advanced renal cell carcinoma (aRCC) with non–ccRCC or RCC with sarcomatoid histology in a Phase II study. In this study, 42 patients had non–ccRCC histology, including papillary, chromophobe, unclassified, and others with or without sarcomatoid component. The ORR in papillary was 26% while it was 10% in chromophobe (McGregor et al. 2020). In addition, Study WO29637 (IMmotion151) subgroup analysis for RCC with sarcomatoid component showed longer PFS in patients receiving atezolizumab in combination with bevacizumab compared with sunitinib (median PFS 8.3 months [95% CI: 5.4–12.9 months] vs. 5.3 months [95% CI: 3.3–6.7 months]; Rini et al. 2019a).

1.5 BACKGROUND ON CABOZANTINIB

Cabozantinib is an orally bioavailable TKI with potent activity against MET and VEGFR2, as well as a number of other receptor tyrosine kinases that have also been implicated in tumor pathobiology, including RET, KIT, AXL, and FLT. Cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models (Sennino et al. 2009; Yakes et al. 2011).

Cabozantinib has shown efficacy in patients with aRCC previously treated with VEGF-targeted therapies as well as treatment-naive patients with RCC (Choueiri et al. 2017b). The METEOR trial (NCT01865747) was a Phase III study comparing cabozantinib administered 60 mg once a day (QD) versus everolimus in patients with advanced RCC who progressed after a previous VEGFR-TKI treatment. The estimated median PFS was 7.4 months (95% CI: 5.6–9.1 months) with cabozantinib and 3.8 months (95% CI: 3.7–5.4 months) with everolimus (OS HR = 0.58; 95% CI: 0.45–0.75; $p < 0.001$). Median OS was 21.4 months (95% CI: 18.7 months to not estimable) with cabozantinib and 16.5 months (14.7–18.8 months) with everolimus (HR = 0.66; 95% CI: 0.53–0.83; $p = 0.00026$). In this trial, approximately 60% of patients previously received sunitinib, and approximately 40% of patients received pazopanib. Nivolumab was previously used in 5% of patients. Patients who received 1 prior therapy were 71%, while 29% of patients received more than one treatment. In this trial, subgroup analyses showed efficacy across different lines of therapy and different types of prior therapies, including VEGFR-TKIs and immunotherapy. Cabozantinib improved survival in patients previously treated with sunitinib (PFS: HR = 0.43; OS: HR = 0.66) or pazopanib (PFS: HR = 0.67; OS: HR = 0.66) irrespective of the number of previous treatment lines received. Cabozantinib also improved PFS in patients previously treated with ICI compared with everolimus (PFS: HR = 0.22 [95% CI: 0.07–0.65], ORR 22% vs. 0%, OS: HR = 0.56 [95% CI: 0.21–1.52]).

Also, as indicated in Table 1, in the front-line setting, cabozantinib showed superiority against sunitinib in intermediate and poor risk RCC with a median PFS of 8.2 months vs. 5.6 months (HR = 0.66; 95% CI: 0.46–0.95; Choueiri et al. 2017b).

In a retrospective single arm study assessing cabozantinib efficacy in non–ccRCC, cabozantinib was shown to be active with an ORR 27%, PFS of 7 months, and OS of 12 months in these patients. The safety profile is similar to that of the ccRCC population (Chanzá et al. 2019).

Cabozantinib (60 mg, tablets) is approved as a single agent for patients with advanced RCC (Cabometyx® U.S. Package Insert [USPI]), and in combination with nivolumab as first-line treatment for patients with advanced RCC (Cabometyx® USPI), for adult patients with advanced RCC after prior VEGF-targeted therapy or treatment-naïve adult patients with intermediate or poor risk RCC (Cabometyx EMA Summary of Product Characteristics [SmPC]), and for patients with hepatocellular carcinoma who have previously been treated with sorafenib (Cabometyx USPI and EMA SmPC). In addition, cabozantinib (140 mg, capsules) is approved for patients with progressive, metastatic medullary thyroid cancer (Cometriq® USPI and EMA SmPC). The capsule and tablet formulations are not bioequivalent or interchangeable.

*The approval of c*abozantinib for the treatment of aRCC *is* based on the results described in Table 1 and Table 2 as well as in advanced hepatocellular carcinoma after prior sorafenib therapy.

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

1.6 BACKGROUND ON COMBINATION THERAPY OF ATEZOLIZUMAB AND CABOZANTINIB

Although the main anti-tumor efficacy with cabozantinib is driven by anti-VEGF, anti-MET, and other TKIs, cabozantinib also appears to modulate the immune-tumor microenvironment and enhances innate immunity (Patnaik et al. 2017). Cabozantinib showed a reduction of tumor vascularity and improves T-cell infiltration as well as showed a reduction of T regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages when combined with immunotherapy (Kwilas et al. 2014). In addition, a report suggests that cabozantinib in combination with anti–PD-1 treatment suppressed MDSCs, which is known to promote tumor infiltration in prostate cancer (Lu et al. 2017). In summary, cabozantinib promotes an immune-permissive environment that may enhance response to ICIs.

COSMIC-021 (NCT03170960) is a Phase Ib study of cabozantinib in combination with atezolizumab to assess the safety and efficacy of this combination in multiple tumor types, including RCC (i.e., treatment-naive patients with RCC). Patients received either 40 mg or 60 mg of cabozantinib QD orally in combination with 1200 mg of atezolizumab IV Q3W. In the dose-escalation stage, 12 patients with RCC (10 clear-cell and 2 non–clear-cell histology) were enrolled: 6 patients received cabozantinib 40 mg (QD orally) and 6 patients received cabozantinib 60 mg (QD orally) in combination with 1200 mg of atezolizumab IV Q3W for a total of 12 patients. There were no dose-limiting toxicities (DLTs) observed at either dose level. As of 21 August 2018, with a median follow-up of 33.4 weeks (range: 26–50 weeks), most adverse events were of Grade 1 or 2, including immune-related adverse events. Grade 3 adverse events included 5 events of hypertension, 2 events each of diarrhea and hypophosphatemia, 1 event each of ALT, AST, lymphopenia, hyperglycemia, gamma-glutamyl transferase (GGT) increased, pulmonary embolism (PE), oral pain, myositis, and lipase increased. There were no Grade 4 or 5 adverse events. Among 12 patients, investigator-assessed confirmed ORR was 67% (1 CR, 7 PRs); 4 additional patients had stable disease with a disease control rate of 100% (Agarwal et al. 2018). Based on a favorable safety profile and encouraging anti-tumor activity, cabozantinib 40 mg in combination with atezolizumab 1200 mg was selected as the recommended dose for expansion cohorts in multiple solid tumor cohorts. Upon evaluation of safety and efficacy data of approximately 30 initially-enrolled patients in an expansion cohort, the Study Oversight Committee could extend enrollment with an additional 30 patients to explore whether cabozantinib 60 mg in combination with atezolizumab will lead to improved clinical efficacy and maintain an acceptable safety profile.

The expansion stage of the COSMIC-021 study has been initiated, enrolling patients across 12 different solid tumor types, including RCC of clear-cell and non–clear-cell histology across all three IMDC risk categories. The ccRCC expansion cohort initially enrolled 30 treatment-naive patients receiving cabozantinib 40 mg in combination with 1200 mg of atezolizumab. Preliminary data of this cohort indicated that the combination therapy was well-tolerated and showed encouraging clinical efficacy.

As of 20 December 2019, 30 patients with ccRCC were enrolled in the cohort receiving 60-mg cabozantinib in combination with atezolizumab. The median follow-up was 7.9 months (range: 3–11 months). Twenty-three (77%) of the 30 patients were actively on study treatment and 7 patients discontinued all study treatment. The reasons for treatment discontinuation were radiographic progression (5 patients), adverse event unrelated to disease progression (1 event), and withdrawal (1 patient). An overview of the efficacy data of the 60-mg cabozantinib RCC cohort is shown in Table 3. The ORR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 was 57% (including 1 CR) and the disease control rate was 89%.

Table 3 COSMIC-021 Study ccRCC Expansion Cohort: Objective Response Rate (per RECIST v1.1) in Cabozantinib 60 mg+Atezolizumab-Treated Patients

Best Response	Cabozantinib 60 mg N = 31 [a] N (%)
ORR, including	17 (57)
Unconfirmed PR	1 (3.3)
CR	1 (3.3)
PR	16 (53)
Stable Disease	10 (33)
Progressive Disease	2 (6.7)
Not Evaluable	1 (3.3)

ccRC = clear-cell renal cell carcinoma; CR = complete response; ORR = objective response rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.
Note: Clinical cutoff date is 20 December 2019.
[a] Evaluable patients are defined as those with at least 1 post-baseline response assessed by the investigator or, if discontinued, prior to assessment.

The most common adverse events of any grade regardless of causality in the 60-mg cabozantinib ccRCC cohort are provided in Table 4. Grade 3 adverse events regardless of causality were observed in 18 patients (60%), the most common of which were ALT increased (13%), hypertension (10%); diarrhea (10%); and hyponatremia (10%). There were 5 Grade 3 immune-related adverse events reported (1 event each of AST increased, lipase increased, immune-mediated enterocolitis, transaminases

increased, and fatigue). There were no Grade 4 or Grade 5 adverse events. Adverse events that led to a dose reduction or treatment discontinuation were observed in 60% and 10% of patients, respectively.

Table 4 COSMIC-021 Study ccRCC Cohort: Summary of Common Adverse Events (≥30% of Patients) in Cabozantinib 60 mg+Atezolizumab-Treated Patients

Adverse Events of any Grade	Cabozantinib 60 mg + Atezolizumab N = 30 N (%)
Palmar-plantar erythrodysesthesia syndrome	15 (50%)
Aspartate aminotransferase increased	14 (47%)
Diarrhea	14 (47%)
Fatigue	14 (47%)
Alanine aminotransferase increased	13 (43%)
Dysgeusia	13 (43%)
Nausea	13 (43%)
Decreased appetite	12 (40%)

ccRC = clear-cell renal cell carcinoma.
Note: Clinical cutoff date is 20 December 2019.

In addition, the COSMIC-021 study is evaluating an expansion cohort of cabozantinib 40 mg in combination with atezolizumab in patients with non–ccRCC. At the cutoff date of 20 December 2019, 30 patients were enrolled. The median follow-up was 6 months (range: 1–13 months). Eighteen patients (60%) were active on study treatment, 7 patients had discontinued all study treatment due to radiographic progression, 5 patients due to other reasons (2 adverse events unrelated to progression, 1 adverse event related to progression, 2 due to lack of clinical benefit). The majority of enrolled patients with non–ccRCC, 25 patients (83%), had not yet received prior systemic therapy. The ORR by the investigator per RECIST v1.1 was 27%. Eight patients exhibited a PR, an additional 2 patients had an unconfirmed PR. Nineteen patients (63%) experienced stable disease; the disease control rate was 90%. The most common adverse events of any grade regardless of causality included diarrhea (37%), palmar-plantar erythrodysesthesia (PPE; 30%), dysgeusia (20%), headache (20%), abdominal pain (17%), amylase increased (17%), AST increased (17%), back pain (17%), fatigue (17%), and nausea (17%). One Grade 4 event of myocarditis (related) was reported, and 2 Grade 5 events (both unrelated, 1 death from RCC progression, 1 event of hemoptysis).

While Study COSMIC-021 is still ongoing, the current results suggest that atezolizumab 1200 mg in combination with cabozantinib 60 mg is tolerable and potentially active in patients with clear-cell and non–clear-cell RCC.

1.7 RATIONALE FOR IMMUNE CHECKPOINT RE-CHALLENGE

There is evidence to support the use of an ICI in combination therapy after progression with a prior ICI. Preliminary efficacy of atezolizumab in combination with bevacizumab in patients treated beyond progression was seen in Study WO29074 (IMmotion150; Atkins et al. 2017). In Study WO29074, patients who progressed on either sunitinib or atezolizumab and had crossed over to the combination of atezolizumab with bevacizumab achieved an ORR of 28% and 24% with a median PFS 8.3 months and 12.6 months, respectively. Similarly, in a cohort of patients with RCC who progressed with prior ICI therapy, pembrolizumab in combination with lenvatinib produced an ORR of 64% with a median PFS by modified RECIST for immune-based therapeutics (iRECIST) v1.1 of 11.3 months (95% CI: 7.3 to not estimable). The most common prior ICI therapies were nivolumab monotherapy, nivolumab/ipilimumab, and avelumab/axitinib (Lee et al. 2019). These results support the hypothesis that ICIs may be effective for patients who experienced progression while on or after receiving ICIs, if combined with different agents. Similar phenomena are being observed across tumor types. Preliminary results from a combination of sitravatinib (multi-TKI of VEGFR2, KIT, MET, AXL, MER, and Tyro) with nivolumab in non-squamous NSCLC after progression while on or after receiving an ICI (Leal et al. 2017) produced an ORR of 32% (including unconfirmed). In addition, mocetinostat (histone deacetylase inhibitor) in combination with durvalumab in patients with NSCLC who have experienced documented disease progression following prior treatment with an ICI (N=29) produced an ORR of 17% (Johnson et al. 2018).

1.8 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

With the rapidly evolving landscape of treatments for metastatic RCC, the use of ICI-based treatments is moving to earlier lines of therapy and is becoming the standard of care for first- and second-line treatments in most countries. Thus, there remains a need to better understand the sequential use of all available RCC treatments and develop effective treatments that fit this evolving landscape (Motzer et al. 2015a; Motzer et al. 2018b; Motzer et al. 2019a; Rini et al. 2019a). A Phase II study of lenvatinib in combination with pembrolizumab has already shown promising activity in patients with prior ICI treatment, supporting the notion of administering an ICI in combination with a VEGFR-TKI in patients previously treated with an ICI.

Both cabozantinib and atezolizumab have shown clinical efficacy in aRCC. Cabozantinib single-agent treatment and treatment with atezolizumab in combination with bevacizumab have shown clinical efficacy in the post-ICI setting in subgroup analyses of prior studies as described in previous sections. These 2 agents are also active for patients with clear as well as non–clear-cell RCC (see Sections 1.4 and 1.5).

The combination of a VEGFR-TKI with immunotherapy may offer an advantage over individual treatment. Cabozantinib contributes to modulation of the immune-tumor microenvironment and may enhance the efficacy of immunotherapy (Kwilas et al. 2014; Lu et al. 2017; Patnaik et al. 2017).

Preliminary results of the administration of the combination of atezolizumab and cabozantinib in treatment-naive patients with aRCC in the COSMIC-021 study suggest that atezolizumab 1200 mg in combination with cabozantinib 60 mg is tolerable with encouraging efficacy, thus warranting further investigation, especially in the patient population with prior ICI treatment. However, given the potential for overlapping toxicities (e.g., diarrhea), an open-label study would allow for better adverse event management. It is anticipated that atezolizumab administered in combination with cabozantinib will have a manageable safety profile and has an acceptable benefit–risk balance to justify the conduct of the study.

Cabozantinib is an already approved and established therapy for the treatment of RCC (METEOR [NCT01865747] and CABOSUN trials [NCT03541902]). The single cabozantinib control arm allows for an evaluation of the contribution of atezolizumab in the combination treatment (experiment arm).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab when given in combination with cabozantinib compared with cabozantinib alone in patients with advanced clear-cell or non–clear-cell RCC (papillary*, chromophobe or* unclassified only) who experienced radiographic tumor progression during or after ICI treatment in the *adjuvant and/or locally advanced/*metastatic setting. Patients with RCC with sarcomatoid features are also allowed into this study. *Patients with the chromophobe subtype of non–clear-cell RCC must have sarcomatoid differentiation.*
Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab in combination with cabozantinib or cabozantinib monotherapy).

2.1 EFFICACY OBJECTIVES

Response will be assessed according to RECIST v1.1 (see Appendix 3).
Objective response at a single timepoint will be determined by the investigator and Independent Review Facility (IRF) according to RECIST v1.1. Objective response per iRECIST (see Appendix 4) may be calculated programmatically by the Sponsor on the basis of the investigator assessments of individual lesions at each specified timepoint.

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone in the ITT population based on the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1, as assessed by an IRF (e.g., IRF-PFS) or death from any cause, whichever occurs first
- Overall survival, defined as the time from randomization to death from any cause

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- PFS assessed by the investigators (investigator-assessed PFS), defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1 or death from any cause (whichever occurs first)
- Investigator- and IRF-assessed ORR (investigator-assessed ORR and IRF-assessed ORR), defined as the proportion of patients with a CR or PR on two consecutive occasions at least 4 weeks apart according to RECIST v1.1
- Investigator- and IRF-assessed duration of response (investigator–assessed-DOR and IRF-DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) according to RECIST v1.1

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- PFS, OS, and ORR in subgroups, defined by demographic and baseline characteristics (e.g., PD-L1 status, prior VEGFR-TKI use, most recent ICI therapy [*adjuvant vs.* first-line vs. second-line], tumor histology, or IMDC risk group)
- Time to response
- Time to *confirmed* deterioration of disease-related symptoms, defined as the time from randomization date to the date of a patient's first ≥4-point score decrease from baseline *on* the Functional Assessment of Cancer Therapy–Kidney Symptom Index 19 (FKSI-19) Disease-Related Symptom-Physical (DRS-P) scale (Appendix 7) *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*
- Change from baseline in patient-reported disease-related symptoms by visit, measured with use of the FKSI-19 DRS-P scale

- Time to *confirmed* deterioration of physical functioning, defined as the time from randomization date to the date of a patient's first ≥10-point score decrease from baseline *on* the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30) physical functioning scale *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*
- Time to *confirmed* deterioration of global health status*/quality of life (GHS/QoL)*, defined as the time from randomization date to the date of a patient's first ≥10-point score decrease from baseline *on* the EORTC QLQ-C30 *GHS/QoL* scale *held for at least two consecutive timepoints, or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*
- Change from baseline in patient-reported physical functioning and global health status by visit, measured with use of the EORTC QLQ-C30 physical functioning and *GHS/QoL* scales
- Descriptive summary statistics by visit for the remaining FKSI-19 and EORTC QLQ-C30 scales
- Cumulative distribution function curves of score change from baseline to Month 6 for each key scale (FKSI-19 DRS-P, EORTC QLQ-C30 physical function, EORTC QLQ-C30 *GHS/QoL*)

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of atezolizumab in combination with cabozantinib compared with cabozantinib alone on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the overall side-effect burden of atezolizumab in combination with cabozantinib compared with cabozantinib alone from the patient's perspective, on the basis of the following endpoint:

- Patient-reported overall bother with treatment side effects during study treatment, measured with use of the FKSI-19 GP5 item

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab and cabozantinib administered in combination on the basis of the following endpoints:

- Atezolizumab concentrations at specified timepoints
- Cabozantinib concentrations at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and demographics, efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to atezolizumab in combination with cabozantinib or cabozantinib alone (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab in combination with cabozantinib or cabozantinib alone, can provide evidence of atezolizumab in combination with cabozantinib or cabozantinib alone efficacy (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood, tumor tissue*, and urine* (listed in Section 4.5.7) and efficacy, PK, immunogenicity, or other biomarker endpoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with atezolizumab in combination with cabozantinib compared with cabozantinib alone to inform economic modeling on the basis of the following endpoint:

- Change from baseline in the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and visual analog scale (VAS) scores by visit

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab given in combination with cabozantinib versus cabozantinib alone in patients with inoperable, locally advanced, or metastatic RCC who experienced radiographic tumor progression during or after ICI treatment in the *adjuvant and/or locally advanced/*metastatic setting. The study will enroll approximately 500 patients at approximately 140–180 sites globally.

Key inclusion criteria include (for more details please see Section 4.1.1):

- Male and female patients aged ≥18 years with Karnofsky Performance Status (KPS) score ≥70 who have histologically-confirmed locally advanced or metastatic clear-cell or non–clear-cell RCC (papillary*, chromophobe, or* unclassified only)

  Sarcomatoid features are allowed. *Patients with the chromophobe subtype of non–clear-cell RCC must have sarcomatoid differentiation.*

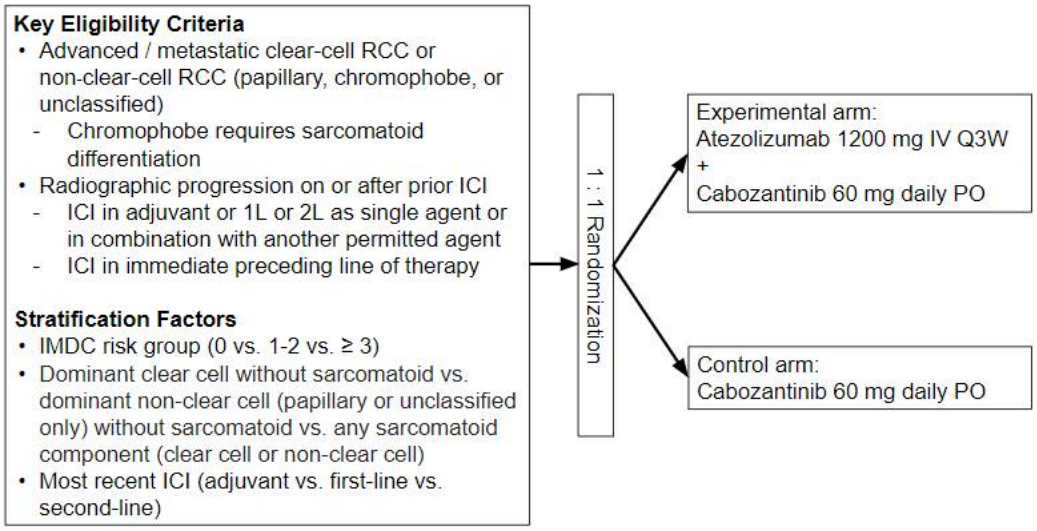
  *Other subtypes of n*on–clear-cell *RCC* (e.g., *collecting duct carcinoma, renal medullary carcinoma*) are not eligible.

- *Patients who have experienced radiographic tumor progression during or following ICI treatment for locally advanced or metastatic RCC either in first-line or second-line treatment. Patients who experienced radiographic tumor progression during or within 6 months after last dose of adjuvant ICI are also eligible.*

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



1L first-line (treatment); 2L = second-line (treatment); ICI = immune checkpoint inhibitor; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PO = by mouth; Q3W = every 3 weeks; RCC = renal cell carcinoma.

Patients will be randomized in a 1:1 ratio to one of the following two treatments arms:

- Experimental arm: Atezolizumab 1200 mg IV infusions Q3W on Day 1 of each 21-day cycle plus cabozantinib 60-mg oral tablets taken QD (1 cycle = 21 days)
- Control arm: Cabozantinib 60-mg oral tablets taken QD (1 cycle = 21 days)

Randomization will be stratified by:

- IMDC risk groups (*favorable*, intermediate or *poor* risk; 0, 1–2, or ≥3), which comprises the following 6 risks factors: time from diagnosis to systemic therapy, KPS, hemoglobin, corrected calcium, neutrophil and platelet count (see Appendix 12)
- Most recent ICI therapy (*adjuvant vs.* first-line vs. second-line)
- Histology: dominant clear-cell without sarcomatoid versus dominant non–clear-cell (papillary or unclassified only) without sarcomatoid versus any sarcomatoid component (clear-cell or non–clear-cell)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle and cabozantinib will be taken orally at a starting dose of 60 mg/day on Days 1–21 of each 21-day cycle. Patients randomized to the atezolizumab and cabozantinib arm who transiently withhold or permanently discontinue either atezolizumab or cabozantinib may continue on single-agent therapy until disease progression (i.e., patients being withheld from cabozantinib transiently for adverse effects may continue atezolizumab monotherapy and vice versa). Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Sections 5.1.3.1 and 5.1.3.2.

Patients will receive atezolizumab and/or cabozantinib until disease progression per RECIST v1.1, unacceptable toxicity, or symptomatic deterioration attributed to disease progression (e.g., pain secondary to disease or unmanageable ascites) as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline, every 9 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter. Tumor assessments will continue until disease progression as assessed by the investigator per RECIST v1.1 (see Appendix 3) or, for patients who continue study treatment after radiographic disease progression, loss of clinical benefit as determined by the investigator (see Section 3.1 for details). In the absence of disease progression, tumor assessments should continue regardless of whether treatment has been discontinued (e.g., for toxicity) or whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first (see Section 4.5.5 for more details). Following treatment discontinuation (even in the absence of disease progression per RECIST v1.1.), patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first. The following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, date of first dose of agent, date of final dose of agent (or if ongoing), patient's best response, and date of disease progression.

Schedules of activities are provided in Appendix 1 and Appendix 2.

Sites must continue to provide images until the IRF determines disease progression. However, treatment decisions will be made based on investigator assessment of disease progression. Independent Review Facility procedures will be detailed in the IRF Charter.

Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudo progression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab and/or cabozantinib will be permitted to continue treatment, until loss of clinical benefit, if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in KPS that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom other treatment options/standard therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression

Tumor tissue will also be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 (within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner; see Section 4.5.7 for more details). These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab and/or cabozantinib.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Safety data will be reviewed on a periodic basis, approximately every 6 months from the time of enrollment of the first patient until the time of the analysis of the primary efficacy endpoint of PFS according to policies and procedures detailed in an iDMC Charter. No interim efficacy analyses are planned for PFS.

All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center. The safety summaries will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs)/Ethics Committees (ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the required numbers of events for the final analysis of OS in the ITT population has occurred (see Section 6).

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 55 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1–20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Cabozantinib Dose and Schedule

Cabozantinib will be administered orally at a starting dose of 60 mg/day starting on Day 1. This is the approved dosage for cabozantinib, as outlined in the Cabometyx™ prescribing information.

From the Phase III METEOR trial (NCT01865747) of cabozantinib in patients with RCC, exposure-response analyses have shown that the 60-mg starting dose would provide greater anti-tumor activity compared with starting doses at 40 mg or 20 mg (Lacy et al. 2018). In the Phase Ib COSMIC-021 study (NCT03170960), no DLTs were observed in either the 40-mg or 60-dose dose-escalation cohorts. As described in Section 1.6, among the 12 patients enrolled in the dose-escalation stage, the investigator-assessed confirmed ORR was 67%. When looking at each dose cohort separately, the ORR for patients with RCC treated with 40 mg cabozantinib was 50% (1 CR and 2 PRs in 6 patients) and 83% (5 PRs in 6 patients) at 60 mg (Agarwal et al. 2018). When looking at the total population of patients in the dose-escalation stage (6 patients at each dose level of 40 mg and 60 mg) and the expansion stage (30 patients at each dose level of 40 mg and 60 mg), the totality of the efficacy data in patients with RCC suggests greater efficacy in the 60-mg patient cohort compared with the 40-mg cohort, with manageable safety profiles at either dose level.

To optimize the benefit of the combination therapy for patients with aRCC, a starting dose of 60 mg cabozantinib (as per the current recommended dose as monotherapy) was selected in combination with atezolizumab for this trial. Dose reductions are allowed to manage side effects according to guidelines outlined in Appendix 11.

Please refer to the Cabozantinib Investigator's Brochure for details.

3.3.3 Rationale for Patient Population

Immunotherapy with ICIs have become standard of care in aRCC. Currently available data in the pre-treated population do not reflect this evolving landscape and; therefore, there is no established treatment paradigm for patients who have previously been treated with an ICI. In addition, it is critical to understand whether immunotherapy can be used again after progression, and whether the sequential use of different immunotherapies, when combined with other agents, is beneficial. Therefore, the study will enroll patients who have progressed on an ICI as their most recent prior therapy in the aRCC setting. However, since ICIs are used both in the front-line and second-line treatment setting, this study will allow up to two prior lines of therapy. Vascular endothelial growth factor receptor-TKIs are used in the front and subsequent lines of therapy either as a single agent or in combination with ICIs. Therefore, this study will include patients who have previously received such TKIs, provided that the therapy preceding trial enrollment is an ICI. However, this study will exclude patients who have previously received a mammalian target of rapamycin (mTOR) inhibitor to reduce heterogeneity in the patient population and to enable the assessment of the scientific hypothesis driving this study.

As seen in the Phase III studies of the combination of pembrolizumab with axitinib or avelumab with axitinib, benefit of the ICI in combination with the VEGFR-TKI was seen regardless of PDL-1 expression (Rini et al. 2019b). Therefore, this study will enroll patients with RCC regardless of tumor PD-L1 status. The PD-L1 status is not expected to impact treatment efficacy for either cabozantinib monotherapy or atezolizumab in combination with cabozantinib treatment. However, archival tumor tissue and fresh samples collected at baseline (if feasible) will be evaluated for potential impact on outcomes.

This trial will enroll patients with both ccRCC and non–ccRCC. Clinical trial data for non–ccRCC are limited since these patients are often excluded from clinical trials. There is preliminary data showing the benefit of atezolizumab as well as cabozantinib in this subtype of RCC, both in trials of these individual agents and also in combination as seen in the non–ccRCC cohort of the COSMIC-021 study (see Sections 1.4 and 1.5). In addition, both nivolumab and pembrolizumab have shown efficacy in non–ccRCC with an ORR of 20–25%, demonstrating the efficacy of immunotherapy in non–ccRCC (Koshkin et al. 2018; McDermott et al. 2019).

However, as seen in all immunotherapy trials mentioned above, including with the combination of atezolizumab with bevacizumab, the ORR in the chromophobe subtype of non–ccRCC have much lower responses (0–10%) than other subtypes. Due to the perceived lack of benefit of immunotherapy *in* the chromophobe subtype*, and the benefit of ICI therapy in sarcomatoid subtypes (Rini et al. 2019a and 2019b), only the chromophobe subtype with sarcomatoid differentiation will be allowed in the study.*

3.3.4 Rationale for Control Group

There is currently no approved treatment or well-recognized standard of care for patients with aRCC who have progressed during or after receiving ICI-based treatment (with or without VEGFR-TKI treatment). The use of a VEGFR-TKI after first-line treatment with ipilimumab/nivolumab in patients with aRCC was reported in a subset of the CheckMate 214 study (NCT02231749) patients (N = 33). A best response of 36% (i.e., unconfirmed) was reported (Auvray et al. 2019), suggesting that VEGFR-TKI is an option after receiving first-line ICI-based treatment.

Although the use of ipilimumab/nivolumab and ICI + VEGFR-TKIs as first-line treatment for patients with aRCC continues to increase, pazopanib and sunitinib (VEGFR-TKIs) are still frequently used as initial treatment. Thus, use of pazopanib and sunitinib would not be appropriate as a comparator for patients in second- or third-line therapy in the proposed Study WO41994. The increasing use of axitinib in combination with ICI-based combinations in the initial treatment of aRCC, also reduces the suitability of this VEGFR-TKI as a control arm in this second- or third-line patient population (Motzer et al. 2019b; Rini et al. 2019a). In addition, both cabozantinib and nivolumab have shown superior efficacy to the standard of care second-line agent everolimus (Motzer et al. 2015a; Choueiri et al. 2016) and; therefore, everolimus is also not the ideal control arm in this study.

Cabozantinib 60 mg QD oral dose has a broad indication for use in patients with aRCC in the United States. In the European Union, cabozantinib is approved for use in adult patients with aRCC as first-line treatment for intermediate or poor risk disease and following prior VEGFR-TKI treatment (regardless of risk category). Given the clinical efficacy data in this study population described in Sections 1.4.1 and 3.3.3, cabozantinib is the ideal choice for a control arm for this study population, especially since the safety and efficacy of this agent in combination with atezolizumab has already been tested.

3.3.5 Rationale for Stratification Factors

Clinical factors known to affect outcomes in aRCC were chosen as stratification factors. In the IMDC risk model (Heng et al. 2009), six risk factors were identified as being associated with poorer survival: time from diagnosis to treatment of less than 1 year, KPS < 80%, neutrophils greater than upper limit of normal (ULN), platelets > ULN, corrected calcium > ULN, and hemoglobin less than lower limit of normal. Three risk categories associated with different outcomes were identified based on these risk factors: favorable risk (0 risk factors) with a median OS (mOS) not reached, intermediate risk (1–2 risk factors) with a mOS of 27 months, and poor risk (3–6 risk factors) with an OS of 8.8 months.

As described in Section 1.3, the proportion of patients receiving third-line therapy is much less than second-line therapy. In addition, outcomes in third-line therapy are worse. Therefore, stratification by line of therapy is important in this study which plans to enroll patients in second- and third-line therapy. Since only patients whose immediate preceding therapy was an ICI are eligible, the difference in line of therapy (second-line or third-line) will be represented by the most recent ICI (*adjuvant or* first-line or second-line).

Several Phase III trials in the adjuvant setting with ICIs such as CheckMate 914 (NCT03138512), IMmotion010 (NCT03024996), KEYNOTE 564 (NCT03142334), PROSPER RCC (NCT03055013) and RAMPART (NCT03288532) are ongoing. Thus, ICIs are heading to become standard of care in the adjuvant setting for patients with RCC. In oncology, patients who progress soon after adjuvant therapy are considered as those with underdiagnosed metastatic disease and hence are commonly included in trials evaluating a refractory population. Progression during or within 6 months after last dose of adjuvant setting is commonly applied in these trials (Rittmeyer et al. 2017; Le et al. 2019; NCT04740918). A similar approach will be adopted for this study.

As described in Section 3.3.3, this study will enroll both clear-cell and non–clear-cell histology. The advances made with VEGFR-directed therapies in ccRCC have only produced modest outcomes in non–ccRCC (Zhang et al. 2017). Sarcomatoid histology is a feature associated with up to 20% of RCCs (Zhang et al. 2017) and has a poor prognosis with VEGFR-directed therapies. Given that the outcomes of non–ccRCC and sarcomatoid RCC are worse than ccRCC, the study will use a stratification factor of histology incorporating both cell type (ccRCC or non–ccRCC) and any sarcomatoid component. It is worthwhile to note that ICIs appear to have a better outcome in the sarcomatoid variant than in VEGFR-directed therapies as seen in subgroup analyses of the study evaluating atezolizumab and bevacizumab compared with sunitinib (Rini et al. 2019a) and the study evaluating pembrolizumab and axitinib compared with sunitinib (Rini et al. 2019b).

3.3.6 Rationale for Open-Label Study

An open-label study design was chosen for this trial due to the expectation of overlapping toxicities that may require significant unblinding to differentiate and manage toxicities.

To ensure the validity of data collected in an open-label study, the primary efficacy analyses will be based on IRF assessment of progression. To avoid aggregated data review of efficacy in each arm during the conduct of the study, the Sponsor will be blinded. In addition, the strategy and timing for the final analysis of the primary endpoint, including censoring rules and methods for handling missing data, have been prespecified in the protocol.

3.3.7 Rationale for Progression-Free Survival and Overall Survival as Multiple Primary Endpoints

In this study, the multiple primary efficacy endpoints will be IRF-assessed PFS and OS. This study will test the hypothesis that treatment with atezolizumab in combination with cabozantinib will prolong PFS and OS compared with treatment with cabozantinib alone.

Overall survival is considered the most reliable endpoint for demonstrating clinical benefit for cancer drugs. However, OS may be potentially confounded by subsequent therapies. Progression-free survival as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit (U.S. Food and Drug Administration [FDA] Guidance 2018). Additionally, PFS has proven to be a reasonable surrogate for clinical benefit in various indications for TKIs: crizotinib and osimertinib have been approved by regulatory agencies for previously treated patients with advanced NSCLC based on an increase in PFS (Xalkori® USPI and European Medicines Agency [EMA] SmPC; Tagrisso® USPI and EMA SmPC); cabozantinib has been approved by regulatory agencies for previously treated patients with advanced RCC based on an increase in PFS (Cabometyx USPI and EMA SmPC). Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit–risk profile of the new treatment compared with available therapies (EMA Guidance 2017; FDA Guidance 2018).

3.3.8 Rationale for Atezolizumab or Cabozantinib Treatment beyond Initial Radiographic Progression per RECIST v1.1

In studies of immunotherapeutic agents, CR, PR, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudo progression (Hales et al. 2010).
In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed intracellular staining and no viable cancer cells.

In addition, radiographic disease progression may not be correlated with clinical conditions. Instead, clinical benefit per the investigator can be used to inform whether continued study treatment is an acceptable risk. The continuation of cabozantinib treatment after radiographic progression is consistent with the prescribing information and was permitted in single-agent trials.

For these reasons, this study will allow all patients to continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 3.3.8). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.3.9 Rationale for the Use of iRECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the efficacy of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, in addition to the traditional RECIST v1.1, this study may employ iRECIST (Seymour et al. 2017; see Appendix 4), tumor response criteria that have been modified for unconventional tumor change patterns associated with cancer immunotherapy.

iRECIST was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials (Seymour et al. 2017). iRECIST accounts for responses that may occur following transient radiographic progression caused by immune-cell infiltration in tumors (leading to a transient increase in the size of existing lesions, including those that were previously undetectable and consequently appear as new lesions). iRECIST relies on collection of tumor assessment data after initial disease progression per RECIST v1.1.

Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, analyses based on iRECIST may be considered. These analyses will allow for evaluation of iRECIST as an improved measure of the efficacy of immunotherapies relative to the standard RECIST v1.1.

3.3.10 Rationale for Clinical Outcome Assessments

Patient experience data will be collected in this study to inform the benefit–risk profile of atezolizumab in combination with cabozantinib. It is important that the addition of atezolizumab to cabozantinib can provide survival benefit and delay disease progression without impairing patients' functioning and quality of life. As such, the patient's perspective on symptom and treatment burden, including physical functioning and treatment toxicity impacts, is needed to achieve a comprehensive evaluation of clinical benefit.

Patient-reported outcome (PRO) instruments in this study will provide a better understanding of the impacts of disease and treatment on patients. The FKSI-19 (Rao et al. 2009; Rothrock et al. 2013) is a validated disease-specific instrument that measures RCC-related symptom burden and health-related quality of life in patients with kidney cancer. The FKSI-19 GP5 item is a valid summary measure of overall treatment side-effect burden in cancer that complements clinician-reported safety.
The EORTC QLQ-C30 (Aaronson et al. 1993; Fitzsimmons et al. 1999) is a validated instrument that has been widely used in assessing the quality of life in patients with cancer. This instrument assesses global health status, functioning (physical, role, emotional, cognitive, and social), and symptoms associated with cancer and its

treatment (e.g., fatigue). The EQ-5D-5L (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) is a generic health status questionnaire that will primarily be used to inform health economic modeling.

3.3.11 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, any tumor samples collected may be tested for PD-L1 expression by a central laboratory. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit and safety of atezolizumab and cabozantinib, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed. DNA and/or RNA extraction and analysis may be performed to enable next-generation sequencing (NGS), including, but not limited to, whole-exome sequencing (WES), to evaluate expression of genes to assess their association with efficacy, and to identify somatic mutations to increase understanding of disease pathobiology.

Blood *and urine*-based biomarkers (including, but not limited to, circulating tumor DNA [ctDNA]) may be also evaluated and correlated with atezolizumab and cabozantinib efficacy and evaluated as potential surrogate markers of efficacy. This evaluation of blood *and/or urine*-based markers may provide evidence for the biologic activity of atezolizumab and cabozantinib in patients with RCC, help to identify patients who may benefit most from atezolizumab and cabozantinib, and help future development of tissue-free diagnostic options for patients who have inadequate quality or insufficient quantity of tumor tissue for biomarker testing.

Blood *and urine* samples will be collected in order to better understand the changes in biomarker profiles and potential mechanisms of resistance upon progression. Blood samples may also be evaluated for additional exploratory biomarkers that may be associated with the therapeutic effects of atezolizumab and cabozantinib or the pathogenesis of RCC.

Tissue samples will be collected for DNA extraction to enable WES to identify variants that are predictive of response to study drugs, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-exome sequencing provides a comprehensive characterization of the exome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be

analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 500 patients will be enrolled in this study. Patients with *locally* advanced or metastatic RCC with clear-cell, or non–clear-cell (papillary*, chromophobe, or* unclassified only) histology, and previously treated with an ICI in the *adjuvant and/or locally advanced/*metastatic setting will be enrolled. Patients with RCC with sarcomatoid features are also allowed in this study. *Patients with the chromophobe subtype of non–clear-cell RCC must have sarcomatoid differentiation.*

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically-confirmed locally advanced or metastatic clear-cell or non–clear-cell (papillary*, chromophobe,* unclassified only) RCC
  - *Other subtypes of n*on–clear-cell RCC (*e.g., collecting duct carcinoma, renal medullary carcinoma*) are not eligible.
  - R*CC* with sarcomatoid features is allowed. *Patients with the chromophobe subtype of non-clear-cell RCC must have sarcomatoid differentiation* (see Appendix 13 for further guidelines regarding the definition of sarcomatoid histology).
- Radiographic disease progression *to prior ICI therapy for* RCC
  - *ICI for metastatic disease: Radiographic disease progression during or following ICI treatment for locally advanced or metastatic RCC either in first- or second-line treatment*
  - *ICI for adjuvant therapy: Patients who experienced radiographic tumor progression during or within 6 months after last dose of adjuvant ICI are also eligible*
  - *Examples of ICI regimens include one* ICI *regimen* in first-line treatment (e.g., nivolumab plus ipilimumab, pembrolizumab plus axitinib, axitinib plus avelumab)*, or* second-line treatment (e.g., TKI as first-line treatment and ICI as second-line treatment)

  - ICI is defined by anti–PD-L1 or anti–PD1 antibody, including atezolizumab, avelumab, pembrolizumab, *durvalumab,* or nivolumab. Ipilimumab monotherapy is not considered an anti–PD-L1 or anti–PD1 therapy.
  - *Patients must have received at least 2 cycles of ICI treatment*
  - *ICI must have been used in the immediate preceding line of therapy* (patients with an intervening treatment between ICI and study screening are excluded)
  - *Adjuvant treatment with VEGFR-TKIs, except cabozantinib, is allowed*
- Measurable disease per RECIST v1.1
- Evaluable IMDC risk scores
- Representative pretreatment tumor specimens, for exploratory biomarker research (see Section 4.5.7 for information on suitability of and requirements for tumor specimens)
  - Archival tumor specimen (e.g., at diagnosis, surgery, or prior to initiation of previous line of therapy)
  - Pretreatment tumor tissue from fresh biopsy at screening, if clinically feasible. Biopsies collected via minor surgery must be performed at least 10 days prior to Day 1 of Cycle 1 and must be completely healed before first dose.

    Availability of tissue samples must be confirmed before randomization. Tissue samples must be submitted before or within 4 weeks of randomization. *Both archival and fresh samples are preferred, if feasible.*
- KPS score of ≥ 70
- *Recovery to baseline or Grade ≤ 1 NCI CTCAE v5.0 from toxicities related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable in the opinion of the investigator*
  - *Grade 2 alopecia is allowed for study participation*
  - *Exception: Patients who have received systemic corticosteroids for a prior immune-related adverse event for >30 days consecutively prior to initiation of study treatment are not eligible. Additional criteria on steroid use for prior immune-related adverse events is described in the exclusion criteria.*
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500 cells/μL) without granulocyte colony-stimulating factor support within 14 days prior to Day 1 of Cycle 1
  - Lymphocyte count $\geq 0.3 \times 10^9$/L (300/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion within 14 days prior to Day 1 of Cycle 1
  - WBC counts ≥ 2500 cells/μL

- Hemoglobin ≥ 90 g/L (9 g/dL) (without transfusion within 14 days prior to Day 1 of Cycle 1)
- AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

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

  Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
- Bilirubin $\leq 1.5 \times$ ULN with the following exception:

  Patients with known Gilbert disease: bilirubin $\leq 3 \times$ ULN
- Creatinine clearance ≥ 40 mL/min (calculated with use of the Cockcroft-Gault formula, or based on 24-hour urine collection)
- Albumin ≥ 25 g/L (2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- Proteinuria, as demonstrated by urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol)

- Negative HIV test at screening
- Negative hepatitis B testing at screening:
  - Negative hepatitis B surface antigen (HBsAg) test at screening
  - Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 4 months after the final dose of cabozantinib and for 5 months after the final dose of atezolizumab. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 months after the final dose of cabozantinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Females of childbearing potential who are partners of male patients should also use contraceptive methods with a failure rate of < 1% per year during their male partner's therapy and for at least 4 months after completing therapy. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment with anti-cancer therapy within *14* days prior to initiation of study treatment
- Patients who received cabozantinib at any time prior to screening
- Patients who received more than one ICI treatment *in the locally advanced or metastatic setting* (e.g., pembrolizumab and axitinib as first-line treatment and nivolumab as second-line treatment)
- Patients who received more than two prior lines of therapy in the *locally* advanced or metastatic setting

- Patients who have received a mTOR inhibitor in *any* setting
- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment
  - No evidence of significant vasogenic edema
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord)
  - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- History of leptomeningeal disease
- Uncontrolled tumor-related pain

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Moderate to severe hepatic impairment (Child-Pugh B or C)

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

  Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

- History of malignancy other than renal carcinoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Radiotherapy for RCC within 14 days prior to Day 1 of Cycle 1

  Patients who are receiving single-fraction radiotherapy given for the indication of pain control are eligible.

- Active tuberculosis
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Minor surgeries (e.g., tumor biopsy, placement of vascular access device) should be performed at least 10 days prior to initiation of study treatment. Patients must have complete wound healing from major surgery or minor surgery before randomization. Patients with clinically relevant ongoing complications from prior surgery are not eligible.

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after final dose of atezolizumab and 4 months after final dose of cabozantinib

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose systemic immunosuppressant medication (e.g., $\leq$10 mg/day oral prednisone or equivalent) or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are eligible for the study.

- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Current treatment with anti-viral therapy for HBV or HCV
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, vasculitis, or glomerulonephritis, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$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

- *Pharmacologically uncompensated, symptomatic hypothyroidism*
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- *Malabsorption syndrome*
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment
- *Tumors invading the GI-tract, active peptic ulcer disease, acute pancreatitis, acute obstruction of the pancreatic or biliary duct, appendicitis, cholangitis, cholecystitis, diverticulitis, gastric outlet obstruction, or inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)*
- Stroke (including transient ischemic attack), myocardial infarction, or other symptomatic ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT], PE) within 6 months before *randomization*

  Upon Sponsor approval, subjects with a diagnosis of incidental PE or DVT within 6 months are allowed if asymptomatic *and stable at screening* treated with low–molecular-weight heparins (LMWHs) or *the direct factor Xa inhibitors* rivaroxaban, edoxaban, or apixaban for at least 1 week before first dose.
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, *unstable arrhythmia, or unstable angina*) within 3 months prior to initiation of study treatment
- History of clinically significant ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History of congenital QT syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction that is considered as clinically significant by investigator
- QT interval corrected with use of Fridericia's formula (QTcF) > 480 ms per ECG within 14 days before randomization

Note: If a single ECG shows a QTcF with an absolute value > 480 ms, 2 additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of the 3 consecutive results for QTcF must be ≤ 480 ms for the patient to be eligible.

- Significant vascular disease (e.g., aortic aneurysm *or arterial dissection* requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy
- Abdominal or tracheoesophageal fistula*, bowel obstruction,* or gastrointestinal (GI) perforation*, or intra-abdominal abscess* within 6 months *before initiation of study treatment*

  Complete healing of an intra-abdominal abscess must be confirmed before initiation of study treatment.
- Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel)

  The following are anticoagulants allowed in this study:

  Prophylactic use of low-dose aspirin for cardio protection (per local applicable guidelines) and low-dose LMWHs.

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in patients without known brain metastases who are on a stable dose of the anti-coagulant for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
- Clinical signs or symptoms of GI obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- *Known cavitating pulmonary lesion(s) or known endobronchial disease manifestations*
- *Lesions invading major pulmonary blood vessels*
- *Clinically significant hematuria, hematemesis, hemoptysis of >0.5 teaspoon (2.5 mL) of red blood, coagulopathy, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before initiation of study treatment*
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Prior history of hypertensive crisis or hypertensive encephalopathy
- *Requirement for hemodialysis or peritoneal dialysis*
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known allergy or hypersensitivity to any component of the cabozantinib formulation
- Patients who are not able to swallow a tablet

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or Web-based response system (IxRS).

Patients will be randomly assigned to 1 of 2 treatment arms: atezolizumab and cabozantinib or cabozantinib alone. Randomization will occur in a 1:1 ratio with use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- IMDC score (0 vs. 1–2 vs. ≥ 3)
- Most recent ICI therapy ($adjuvant\ vs.$ first-line vs. second-line)
- Histology: dominant clear-cell without sarcomatoid versus dominant non–clear-cell (papillary or unclassified only) without sarcomatoid versus any sarcomatoid component (with clear-cell or non–clear-cell)

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and cabozantinib. The first dosing day (Day 1 of Cycle 1) should occur within 3 days from the date of randomization.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

The dose of atezolizumab to be used in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion Q3W (21 [± 3] days).

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.1.2 Cabozantinib

The comparator of this study is cabozantinib 60 mg (three 20-mg tablets) administered orally QD. Cabozantinib will be supplied by the Sponsor as 20-mg yellow film-coated tablets. For information on the formulation and handling of cabozantinib, see the pharmacy manual and the Cabozantinib Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Sections 4.3.2.1 and 4.3.2.2.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 10 and Appendix 11.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Atezolizumab infusions will be administered per the instructions outlined in Table 5.

Table 5 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion • Atezolizumab should be infused over 60 (±15) minutes • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator • Vital signs should be measured within 60 minutes prior to the infusion • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 10.

No dose modification for atezolizumab is allowed.

4.3.2.2 Cabozantinib

Cabozantinib will be taken orally 60 mg QD until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1 for details).

First Dose of Cabozantinib

The first dose of cabozantinib (on Day 1 of Cycle 1) will be administered in the clinic. For patients assigned to the atezolizumab and cabozantinib arm, atezolizumab will be administered first.

The patient will fast (with the exception of water) for at least 2 hours before receiving cabozantinib. Upon completion of the 2-hour fast, the patient will receive the oral dose of cabozantinib with a minimum of 8 oz (240 mL) of water in the clinic and then the patient will continue to fast for 1 hour.

Subsequent Dose of Cabozantinib

Following the first dose of cabozantinib, the patient should take cabozantinib outside the clinic at approximately the same time QD, preferentially before going to bed, and should adhere to the fasting requirements described in this section.

Patients should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose. After the 2-hour fast and before going to bed, patients are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for 1-hour postdose. If the patient's schedule requires taking cabozantinib during the day, the patient is to be instructed to follow the same fasting recommendations.

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

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

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

4.3.3 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab and cabozantinib. All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab and Cabozantinib

The Sponsor will offer continued access to study treatment (atezolizumab and cabozantinib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive atezolizumab and cabozantinib after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive atezolizumab and cabozantinib after completing the study if any of the following conditions are met:

- The study treatment is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for RCC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for RCC
- Provision of the study treatment is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)
- Hormone replacement therapy
- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:

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

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban at the time of the first dose of study treatment are allowed if the patient has no evidence of brain metastasis, has been on a stable dose of the anti-coagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
  Note: Anticoagulation with the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor betrixaban is not allowed.

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban after first dose of study treatment are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the investigator's discretion.
  Note: Anticoagulation with the direct thrombin inhibitor dabigatran or the direct factor Xa inhibitor betrixaban is not allowed.

  Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, patient education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as GI cancers, urothelial cancers, GI mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of GI bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as GI absorption, should be considered. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) shouldn't be used concomitantly with heparin or factor Xa inhibitors due to the increased risk for bleeding complications.
  The risks and benefits of the use of anticoagulants should be re-assessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anti-coagulant and accepted clinical practice guidelines.

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

- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known *bone* metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and/or cabozantinib may be continued during palliative radiotherapy.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of 3 or fewer lesions may still be eligible to continue study treatment after Medical Monitor approval has been obtained. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2, 4.4.3, and 4.4.4) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 9).

4.4.2 Cautionary Therapy for All Patients

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.3.1 Corticosteroids, *Immunosuppressive Medications,* and TNF-α Inhibitors

Systemic corticosteroids, *immunosuppressive medications,* and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, *immunosuppressive medications,* or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, *immunosuppressive medications,* and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Appendix 10 for details).

4.4.4 Cautionary Therapy for Cabozantinib-Treated Patients

4.4.4.1 Cytochrome P450

Data from a clinical drug interaction study (XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the concentration–time curve (AUC) of coadministered 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]/inhibition constant values compared with CYP2C8 (i.e., 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 coadministration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution

because these drugs have the potential to decrease exposure (i.e., AUC) to cabozantinib. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a patient who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure 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. Coadministration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. 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 (i.e., AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Grapefruit and Seville oranges (and products made from them) should be avoided while being treated with cabozantinib.

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

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

4.4.4.2 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 coadministered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

4.4.4.3 Concomitant Medications that are Known to Prolong the Corrected QT Interval

Concomitant medications that are known to prolong the corrected QT interval (QTc) should be avoided in patients who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to https://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc).

4.4.4.4 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 (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, 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 (e.g., cyclosporine, efavirenz, emtricitabine) should be approached with caution. Additional details related to these overall conclusions can be found in the Atezolizumab 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 (i.e., PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in patients administered cabozantinib.

Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure and should be avoided.

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

4.4.5 Prohibited Therapy for All Patients

Use of the following concomitant therapies is prohibited for all patients:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment (see Section 4.4.1 for details, with the exception of palliative radiotherapy)
- Any investigational therapy is prohibited within 4 weeks prior to initiation of study treatment and during study treatment

4.4.6 Prohibited Therapy for Atezolizumab-Treated and Cabozantinib-Treated Patients

Use of the following concomitant therapies is prohibited for patients treated with atezolizumab and cabozantinib:

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab
- Oral anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low-dose levels for cardio protection per local applicable guidelines), until 4 weeks after cabozantinib has been permanently discontinued (for permitted anticoagulants, see Section 4.4.1)

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Evaluations (e.g., tumor imaging) 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.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Certain laboratory values must be obtained closer to randomization, within 14 days. The investigator will maintain a screening log to record

details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, IMDC risk assessment, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. The limited physical examination must be performed within 96 hours prior to administration of drug. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic BP, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 6 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 9 weeks (±7 days) for the first 18 months following treatment initiation, and every 12 (±7 days) weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue study treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.
All patients, regardless of arm, will also undergo a follow-up post-disease progression tumor assessment after investigator assessment of radiographic disease progression per RECIST v1.1. When feasible, this subsequent scan will take place on the same schedule as prior to progression (at 9 weeks (±7 days) if disease progression occurred in the first 18 months, and at 12 weeks (±7 days) if disease progression occurred after the first 18 months following treatment initiation).

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening providing the images allow a full RECIST evaluation.

Screening assessments must include CT scans (with oral or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed, and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the

investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Objective response per iRECIST (see Appendix 4) may be calculated programmatically by the Sponsor on the basis of investigator assessments of individual lesions at each specified timepoint.

To facilitate evaluation of response per iRECIST, a follow-up post-RECIST v1.1 disease progression-tumor assessment must be performed in both study arms and tumor assessments must be continued until treatment discontinuation for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 4) at all subsequent assessments.

4.5.5.1 Independent Review Facility

An IRF will be used to conduct blinded radiology review of the imaging data and will provide an independent assessment of tumor response and progression for all patients. Independent Review Facility-assessed endpoints will be used for primary and secondary analyses.

All scans must be submitted to an IRF for central review *until IRF determination of progression*.

4.5.6 Survival Assessments

Overall survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months (every 12 weeks [±1 month]) or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival, PROs (for the first 4 survival follow-up visits only), and new anti-cancer therapy information

unless the patient requests to be withdrawn from the survival follow-up (this request must be documented in the source documents and signed by the investigator). If the patient specifically withdraws from survival follow-up, the study staff may use a public information source (e.g., county records), per local regulations, to obtain information about survival status only.

See Appendix 1 for the schedule of follow-up assessments.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if applicable])
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, urate, ALP, ALT, AST, and LDH

  Note: Calculated corrected calcium will be collected at screening.
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, T3 (or total T3 for sites where free T3 is not performed), and T4
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. Hepatitis B virus DNA test must be negative.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at every cycle during study treatment (predose), at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- Urine Chemistry (Protein [spot urine; fully quantitative]; Creatinine [spot urine; fully quantitative]; UPCR [spot urine])

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum sample for analysis of C-reactive protein
- Serum samples for atezolizumab PK analysis through use of a validated assay
- Plasma samples for cabozantinib PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of a validated assay
- Blood, plasma, serum*, and urine* samples for exploratory research on biomarkers and biomarker assay development

  Blood *and urine* samples may be processed to obtain *derivatives, which may include* plasma, serum, peripheral blood mononuclear cells (PBMCs) and other*s* (e.g., RNA, DNA, *ctDNA,* etc.).

- Archival and a newly collected (fresh) tumor tissue sample obtained at baseline (if clinically feasible) that is suitable for exploratory research on biomarkers (e.g., PD-L1 status via central testing), including biomarker assay development.

  Pretreatment tumor biopsies collected via minor surgery must be performed at least 10 days prior to Day 1 of Cycle 1 and must be completely healed before study treatment.

  Representative formalin-fixed, paraffin-embedded tumor specimens in a paraffin block (preferred) or slides (15 or more) containing unstained, freshly cut, serial sections should be submitted. If 15 slides are not available, 10 slides are acceptable with Medical Monitor confirmation.

  Tumor tissue samples must be submitted before or within 4 weeks of randomization.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples should be collected via resection, core-needle biopsy (at least three, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not

preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

An optional tumor biopsy while on treatment is discussed further in Section 4.5.11.

- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible, for exploratory research on biomarkers, including biomarker assay development

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred.

  Cabozantinib must be withheld for biopsies (see Section 4.5.11 for details).

- Exploratory biomarker research may include, but will not be limited to, analysis of proteins, genes or gene signatures associated with tumor immunobiology, PD-L1, markers associated with T-cell activation, or density, localization, and activation status of immune cells and their subsets, and may involve extraction of DNA, ctDNA, or RNA, analysis of somatic mutations, and use of NGS (including, but not limited to, WES)

Screening tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

- Serum samples collected for atezolizumab PK, cabozantinib PK, or atezolizumab immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed
- Blood*, urine,* and tumor samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final CSR has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms and Echocardiograms

An ECG is required at screening, and then prior to Day 1 of treatment cycles as indicated in Appendix 1. If no clinical symptoms were identified at screening, ECG does not need to be repeated on Day 1 of Cycle 1.

Electrocardiograms for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. At screening and during the study, ECGs will be performed with standard 12-lead ECG equipment according to standard procedures to determine the corrected QTc calculated by the QTcF. If at any time a single ECG shows a QTcF with an absolute value $>$480 ms or an increase in the QTcF of $>$60 ms above baseline, 2 additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of these 3 consecutive results for QTcF will be used as the value assessed (see Appendix 8).

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

Abnormalities in the ECG that lead to a change in patient management (e.g., 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 adverse events. If values meet criteria

defining them as serious, they must be reported as serious adverse events (see Section 5.4.2).

The Fridericia formula is depicted below for calculation of the QTcF value.

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

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

Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease. In countries where additional cardiac monitoring is considered standard (e.g., France), additional cardiac monitoring, including baseline evaluation of LVEF in those patients with cardiac risk factors, and/or an abnormal baseline ECG may be performed.

4.5.9 Clinical Outcome Assessments

Patient-reported outcome instruments will be completed to more fully characterize the clinical profile of atezolizumab and cabozantinib. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab and cabozantinib.

Patient-reported outcome data will be collected through use of the following instruments: EORTC QLQ-C30, EQ-5D-5L, and FKSI–19.

Patient-reported outcome instruments will be completed by patients on Day 1 of each cycle for the first 12 cycles and then Day 1 of every other cycle during study treatment, at the end-of-treatment visit, and at 4 subsequent survival follow-up visits. Survival follow-up assessments may be conducted over the telephone.

All patients will complete the EORTC QLQ-C30, FKSI–19, and EQ-5D-5L questionnaires at 3, 6, 9, and 12 months after radiographic disease progression per RECIST v1.1 or (for patients who continue study treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator.

Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the questionnaires at the end-of-treatment visit and then until disease progression when going to the clinic for any study-related assessments.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

Patient-reported outcome instruments will be self-administered at the clinic at specified timepoints during the study and survival follow-up (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments that may bias patient responses, and prior to the administration of study treatment, unless otherwise specified.

Patient-reported outcome instruments, translated into the local language as appropriate, will be completed in pre-printed paper booklets provided by the Sponsor.

Patient-reported outcome instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 23 minutes at each specified visit
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 5). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a

7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

Functional Assessment of Cancer Therapy-Kidney Symptom Index–19

The FKSI-19 is a validated self-report measure (Rao et al. 2009; Rothrock et al. 2013; see Appendix 7). It consists of 19 questions that assess symptoms and QoL in kidney cancer, including these four domains: physical disease-related symptoms (score range: 0–48), emotional disease-related symptoms (score range: 0–4), treatment side effects (score range: 0–12), and function/well-being (score range: 0–12). A total scale score comprising all 19 items can also be derived (score range: 0–76). Each item is scored on a 5-point scale with response categories ranging from “not at all” to “very much.” Higher scale scores indicate lower symptom burden. The patient’s perspective on overall side-effect burden is captured by the GP5 item, where patients self-report how bothered they were by their treatment side effects (Pearman et al. 2018). This standalone item is a valid summary measure of the overall impact of treatment-related toxicities in cancer and complements safety reporting by clinicians. FKSI-19 items can also be rescored to earlier versions of the FKSI, including the FKSI-DRS and the FKSI-15. The FKSI-19 takes approximately 10 minutes to complete.

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 6). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status.
The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.10 Blood Samples for Whole-Genome Sequencing or Whole-Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable whole-genome sequencing (WGS) or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics.
DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.7) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

See Section 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Tumor Biopsies

In addition to collection of baseline tissue, consenting patients will undergo optional tumor biopsies at any time after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Consenting patients may undergo additional on-treatment biopsies at any time at the investigator's discretion (if deemed clinically feasible by the investigator).
Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Optional in-treatment biopsies collected from easily

accessible tumor lesions requiring a minimally invasive approach (skin punch biopsy, percutaneous lymph node or liver biopsy) will require study treatment interruption 48 hours prior to collection. Study treatment should not be resumed until a minimum of 7 days after the in-treatment biopsy, the decision to resume study treatment should be based on clinical judgment of complete wound healing. Biopsies from lesions which require major surgery or are deemed not easily accessible and put a patient at an unacceptable risk from the procedure are not permitted. Tumor tissue from bone lesions is not acceptable unless taken from a soft-tissue component of the bone lesion.

Samples may be used for exploratory biomarker research as described in Section 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides).
The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. Research Biosample Repository samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.7) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab, cabozantinib, diseases, or drug safety:

- Blood *and urine* samples collected predose on Day 1 of Cycle 1 *and anytime thereafter*
- Leftover blood, serum, plasma, PBMC, *urine,* and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Research Biosample Repository samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Research Biosample Repository samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following e-mail address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.12.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients in the experimental arm (atezolizumab in combination with cabozantinib) are allowed to discontinue one component of the study treatment but continue to receive the other component as described in Section 5.1.3 for management of adverse events.

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Disease progression per RECIST v1.1. or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

Patients may choose to withdraw from treatment, the study, or both. Patients who withdraw from treatment are encouraged to continue survival follow-up to gather data which is valuable to the study.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and cabozantinib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1 and Section 5.1.2).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study as indicated below. Administration of atezolizumab and the first dose of cabozantinib will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Subsequent doses of cabozantinib will be self-administered at home (Section 4.3.2.2). Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 10 for atezolizumab and Appendix 11 for cabozantinib. See Sections 5.2–5.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

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.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis*, and severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. See Appendix 10 of the protocol and Section 6.4.1 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Cabozantinib

Cabozantinib has been associated with risks such as the following: GI disorders, non-GI fistula formation, hemorrhage, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, hepatocellular toxicity, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders. See Appendix 11 of the protocol and the Cabozantinib Investigator's Brochure for a detailed description of anticipated safety risks for cabozantinib.

5.1.3 Management of Patients who Experience Adverse Events and Potential Overlapping Toxicities

Atezolizumab and cabozantinib have molecule-specific safety profiles based on their mechanism of action and adverse events that may also overlap. These include, but are not limited to, hepatotoxic, endocrine, GI, dermatologic, neurologic, renal, and pulmonary events, as well as signs and symptoms such as fatigue and, decreased appetite that may be related to multiple system organ class events. The attribution of each drug in certain adverse events may be uncertain when the products are administered as combination treatment and warrant diagnostic work up. For the management of such potentially overlapping adverse events in patients treated with atezolizumab in combination with cabozantinib, adverse events should be managed according to the recommendations in Appendix 10 (atezolizumab), and Appendix 11 (cabozantinib) and applied to the component of the study treatment judged to be the primary cause. If individual component causality for adverse events cannot be determined, conservative management should be followed to include dose modification/interruption of both agents.

Table 7 Guidance for Managing Overlapping Toxicities

Toxicity	Atezolizumab	Cabozantinib
Pulmonary events	Appendix 10, Table 1	Appendix 11, Respiratory Disorders
Hepatic events	Appendix 10, Table 2	Appendix 11, Table 5
Gastrointestinal events	Appendix 10, Table 3	Appendix 11, Table 1
Endocrine events	Appendix 10, Table 4	Appendix 11, Endocrine Disorders
Dermatologic events	Appendix 10, Table 9	Appendix 11, Table 3
Neurologic events	Appendix 10, Table 10	Appendix 11, Nervous System Disorders
Renal events	Appendix 10, Table 12	Appendix 11, Table 4

5.1.3.1 Dose Modification

Atezolizumab

There will be no dose reductions for atezolizumab in this study. For dose interruptions of atezolizumab see Section 5.1.3.2 and Appendix 10.

Cabozantinib

Dose modifications for cabozantinib are as follows:

- Two dose reduction levels of cabozantinib (40 mg QD and 20 mg QD) are permitted (see Table 8)
- Dose modification criteria for treatment-related adverse events of cabozantinib are shown in Table 9
- Dose reinstitution and re-escalation after dose interruptions and/or reductions:

  If the patient recovers from his or her toxicities to Grade ≤ 1 per NCI CTCAE v5.0 or to the baseline value (or lower) and the adverse event was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.

  If the patient recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) and the adverse event was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose (see Table 9). Patients who initiated treatment with cabozantinib at 60 mg and experience a possibly related adverse event 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 adverse event.

Patients receiving a dose of 20 mg QD who have cabozantinib interrupted may be restarted at the same dose if deemed safe at the discretion of the investigator. Patients unable to tolerate a dose of 20 mg QD must discontinue cabozantinib.

Re-escalation to the previous dose may be allowed at the discretion of the investigator but no sooner than 2 weeks beyond resolution of adverse events that led to the dose reduction, which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed following a cabozantinib-related dose reduction for Grade 4 hematologic toxicities or Grade 4 adverse events affecting major organs (e.g., CNS, cardiac, hepatic, renal, pulmonary, GI).

Table 8 Dose Reduction Levels for Cabozantinib (Oral Dosing)

Assigned Starting Dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg QD	40 mg QD	20 mg QD [a]

QD = once a day.

[a] Cabozantinib will be discontinued if a dose of 20-mg QD of cabozantinib is not tolerated.

Table 9 Dose Modifications for Cabozantinib-Related Adverse Events

Grade per NCI CTCAE v5	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 [b] 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 [b] 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: • Patient 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; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once a day.

[a] Cabozantinib will be discontinued if a dose of 20-mg QD of cabozantinib is not tolerated.

[b] Cabozantinib must be interrupted until the adverse event resolves to Grade ≤ 1.
Note: In exceptional cases, treatment with cabozantinib may be continued at a reduced dose (without interruption) if, according to the investigator's judgment, the toxicity can be easily managed with a dose reduction of cabozantinib and optimal medical care.

For guidelines on dose modifications to manage specific adverse events associated cabozantinib treatment, see Appendix 11.

5.1.3.2 Treatment Interruption

Dose interruptions of study treatment may occur at any time and independently at the discretion of the investigator for management of adverse events. If either or both study treatments in the experimental arm (atezolizumab in combination with cabozantinib) are interrupted more than 12 weeks, the Sponsor should be contacted to discuss potential treatment continuation.

Patients in the experimental arm 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.

Atezolizumab treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over 1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for $>$12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit.

For guidelines on treatment interruption to manage specific adverse events associated with atezolizumab and cabozantinib, see Appendix 10 for atezolizumab and Appendix 11 for cabozantinib.

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can; therefore, be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition; see Sections 5.3.5.9 and 5.3.5.10 for more information)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, *IRRs, CRS, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome*
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will assess seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 10 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE v5.0.

Table 10 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 11):

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

Table 11 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only 1 adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

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

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the

Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by 1 adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events that are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of RCC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be

replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Renal Cell Carcinoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

    The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

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

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

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

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

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

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

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).
For atezolizumab or cabozantinib, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

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

- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data *by the Sponsor. Sites are not expected to review the PRO data for adverse events.*

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D. (Primary)

Telephone No.: [redacted]

E-mail:

Medical Monitor: [redacted], M.D. (Secondary)

Telephone No.: [redacted]

E-mail:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators.

5.4.2.2 Events that Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.
Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study and within 5 months after the final dose atezolizumab and 4 months after the final dose of cabozantinib, whichever is later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the final dose of cabozantinib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the

risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo fetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome (see Section 5.4.3)

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Cabozantinib	Cabozantinib Investigator’s Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab plus cabozantinib as compared with cabozantinib monotherapy.

Analysis populations are defined as follows:

- The ITT populations defined as all randomized patients whether or not the assigned treatment was received
- The measurable disease population is defined as patients in the ITT population with measurable disease at baseline
- The DOR population is defined as patients with objective response
- The PRO-evaluable population is defined as patients with a non-missing baseline PRO assessment
- The safety-evaluable population is defined as patients who received any amount of any component of the study treatments

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 500 patients are planned for enrollment globally over 20 months.
The sample size calculation is determined based on the below considerations.

Type I Error Control

The type I error (α) for the entire study is 0.05 (2-sided). There are multiple primary efficacy endpoints for this study: PFS by IRF assessment per RECIST v1.1 and OS in the ITT population. To control the overall type I error rate (Bretz et al. 2009) at $\alpha = 0.05$ while accounting for 2 primary endpoints, α is split between PFS ($\alpha = 0.02$) and OS ($\alpha = 0.03$). The type I error can be recycled (Burman et al. 2009) if PFS results in the ITT population are statistically significant at $\alpha = 0.02$, then $\alpha = 0.02$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$.
The study will be considered as a positive study if statistical significance is achieved in favor of the experimental arm for either of the multiple primary endpoints, since the type I error (α) for the entire study is controlled at 0.05.

Primary Endpoint: Progression-Free Survival by Independent Review Facility Assessment per RECIST v1.1 in the Intent-to-Treat Population

The analysis of the primary endpoint of PFS by IRF assessment per RECIST v1.1 will take place when approximately 325 IRF-assessed PFS events have occurred in the ITT population (65% events patient rate) based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.02$ (2-sided)
- Approximately 90% power

- Median PFS for the cabozantinib arm of 8.0 months and estimated median PFS in the atezolizumab and cabozantinib arm of 11.9 months (corresponding to HR of 0.67)
- 5% annual loss to follow-up for PFS
- No interim analysis

On the basis of these assumptions, it is projected that an observed HR of 0.77 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.77 will be the minimum detectable difference [MDD] for the analysis; this corresponds to an improvement of 2.4 months in median PFS from 8.0 months in the cabozantinib arm to 10.4 months in the atezolizumab and cabozantinib arm).

Primary Endpoint: Overall Survival in the Intent-to-Treat Population

The final analysis of the primary endpoint of OS will take place when approximately 325 OS events have occurred in the ITT population (65% events patient rate) based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.03$ (2-sided)
- Approximately 85% power
- Median OS in the cabozantinib arm of 22 months and estimated median OS in the atezolizumab and cabozantinib arm of 31.4 months (an increase of 9.4 months, corresponding to an HR of 0.70)
- 1% annual loss to follow-up for OS
- Two interim OS analyses

At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.78 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the MDD at the analysis; this corresponds to an improvement of 6.2 months in median OS, from 22 months in the control arm to 28.2 months in the atezolizumab and cabozantinib arm).

Sample Size

With the above assumptions on PFS and OS, the sample size is determined at 500 patients, where the PFS and OS final analysis will be conducted when 325 events occur (65% events patient rate), respectively. The 500 patients are planned for enrollment globally over 20 months.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations, including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm. Study treatment administration and reasons for discontinuation from the study treatment will be summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race/ethnicity, stratification factors (IMDC score, line of therapy, histology), and baseline characteristics will be summarized by treatment arm for the ITT population. Continuous variables will be summarized with use of means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Multiple Primary Efficacy Endpoints

The multiple primary efficacy endpoints are IRF-assessed PFS per RECIST v1.1 and OS.

Progression-free survival is defined as the time from randomization to disease progression, as determined by the IRF per RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date.

Overall survival is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization.

The following analyses will be performed for both PFS and OS endpoints described above. Progression-free survival and OS will be compared between treatment arms with use of the stratified log-rank test at the 2-sided level of significance. The HR with a 95% CI will be estimated with use of a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. The randomization stratification factors are most recent ICI therapy ($adjuvant\ vs.$ first-line vs. second-line), histology (dominant clear-cell without sarcomatoid vs. dominant non−clear-cell [papillary or unclassified only] without sarcomatoid vs. any sarcomatoid component [clear-cell or non−clear-cell]), and the IMDC score (0, 1−2, $\geq$3). If at least 1 stratum has less than 10 events at the time of analysis, the stratification factor that contains the level with the smallest number of patients will be removed from the stratified analyses. The final set of stratification factors used for the multiple primary endpoints will be applied to all other endpoints where stratified analyses are planned. The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the

median PFS and OS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

6.4.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints per RECIST v1.1 will be analyzed:

- Investigator-assessed-PFS
- Investigator- and IRF-assessed ORR
- Investigator- and IRF-assessed duration of objective response

Statistical methods for treatment arm comparison of investigator-assessed PFS as the secondary endpoint will be the same as the methods for treatment comparisons for the primary efficacy endpoint of IRF-PFS.

6.4.2.1 Objective Response Rate

An objective response is defined as either a CR or PR (confirmation is required, i.e., with CR or PR at two consecutive tumor assessments at least 28 days apart) based on RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessments, will be considered non-responders.
Objective response rate is defined as the proportion of patients who had an objective response among patients with measurable disease at baseline. Unconfirmed response rate will also be evaluated.

Objective response rate will be compared between treatment arms with use of the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described in the analysis of the multiple primary efficacy endpoints of PFS and OS. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated with use of the Clopper-Pearson method. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated with use of the normal approximation to the binomial distribution.

6.4.2.2 Duration of Response

Duration of response is defined for patients who had a confirmed objective response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DOR will be censored at the date of the first occurrence of CR or PR.

Duration of response is based on a non-randomized subset of patients (those who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between two arms will be made for descriptive purposes only. Methods for comparison of DOR between treatment arms will

be the same as the methods for treatment comparison for the multiple primary efficacy endpoints of PFS and OS.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Analyses at Landmark Timepoints

The PFS and OS rates at various timepoints (i.e., every 6 months after randomization) will be estimated by the Kaplan-Meier methodology for each treatment arm and the 95% CI will be calculated with use of Greenwood's formula.

6.4.3.2 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics (e.g., PD-L1 status, prior VEGFR-TKI use, most recent ICI therapy (*adjuvant vs.* first-line treatment vs. second-line treatment), tumor histology, or IMDC risk group), PFS, ORR, and OS in these subgroups investigator-assessed DOR and IRF-assessed DOR will be examined. Summaries of PFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median, will be produced separately for each level of the categorical variables. Objective response rate will be summarized for each level of the categorical variables.

6.4.3.3 Time to Response

Time to response is defined as the time from randomization to first response of PR or CR among responders.

6.4.3.4 Time to Deterioration of Disease-Related Symptoms

Time to *confirmed* deterioration of disease-related symptoms is defined as the time from randomization date to the date of a patient's first 4-point or more score decrease from baseline *on* the FKSI-19 DRS-P scale *held for at least two consecutive timepoints or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*. Kaplan-Meier methods will be applied to this endpoint.

6.4.3.5 Time to Deterioration of Physical Functioning

Time to *confirmed* deterioration of physical functioning is defined as the time from randomization date to the date of a patient's first 10-point or more score decrease from baseline *on* the EORTC QLQ-C30 physical functioning scale *held for at least 2 consecutive timepoints or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*. Kaplan-Meier methods will be applied to this endpoint.

6.4.3.6 Time to Deterioration of Global Health Status/*Quality of Life*

Time to *confirmed* deterioration of *(GHS/QoL)* is defined as the time from randomization date to the date of a patient's first 10-point or more score decrease from baseline *on* the EORTC QLQ-C30 *GHS/QoL* scale *held for at least 2 consecutive timepoints or followed by death within 3 weeks (if Cycles 1–12) or 6 weeks (if after Cycle 12) from the last PRO assessment*. Kaplan-Meier methods will be applied to this endpoint.

6.4.3.7 Patient-Reported Outcome Descriptive Summaries

Compliance rates in the ITT population will be calculated as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment at each timepoint for each treatment arm. Reasons for missing assessments, if available, will be summarized with use of frequencies and percentages.

Descriptive analyses will include summary statistics (mean, standard deviation, median, interquartile range [IQR], minimum, maximum) of PRO scores and score changes from baseline at each assessment timepoint by treatment arm. Additional timepoints of interest include PRO score at radiographic disease progression (i.e., a patient's last PRO assessment score within 30 days prior to or on the day of diagnosis of disease progression) and treatment discontinuation due to adverse events (i.e., a patient's last PRO assessment within the 30 days prior to treatment discontinuation due to adverse events). Graphs of mean scores and/or score changes from baseline along with 2-sided 95% CIs may be presented. Descriptive summaries will be reported for the key scales (FKSI-19 DRS-P, EORTC QLQ-C30 physical functioning, and EORTC QLQ-C30 *GHS/QoL*) as well as the remaining FKSI-19 and EORTC QLQ-C30 scales.

Cumulative distribution function plots of score change from baseline to Month 6 by treatment arm will be presented for each key scale (FKSI-19 DRS-P, EORTC QLQ-C30 physical function, EORTC QLQ-C30 *GHS/QoL*).

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least 1 dose of study treatment, with patients grouped according to treatment received.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, Vital Signs, and Data

Safety analyses will be performed on the safety-evaluable population. Specifically, a patient will be included in the atezolizumab and cabozantinib experimental arm in the safety analyses if the patient receives any amount of atezolizumab or cabozantinib, regardless of the initial treatment assignment at randomization.

Safety endpoints will include the incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0, including serious adverse events and adverse events of special interest, and clinical laboratory results following the administration of study drugs. Drug exposure will be summarized, including duration,

dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms and graded according to the NCI CTCAE v5.0. All adverse events will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ADA results, will be summarized by treatment arm. Deaths and causes of deaths will be summarized.

6.5.2 Exploratory Analyses of Patient-Reported Treatment Side-Effect Burden

Descriptive analysis of the patient-reported overall side-effect bother item (FKSI-19 GP5) will be performed by treatment arm at each visit in the safety-evaluable population. Distribution of responses will be summarized as frequencies and percentages. Change from baseline may be summarized as no change; improved by 1, 2, 3, or 4 levels; and worsened by 1, 2, 3, or 4 levels. Stacked bar charts may also be used to illustrate the distribution of responses or the change from baseline at each timepoint by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

Sparse concentrations of atezolizumab and cabozantinib will be reported as individual values and as group descriptive statistics as data allow (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation). The concentration-time course will also be plotted for each drug.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of patients who received any amount of atezolizumab with at least one ADA assessment for atezolizumab.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of 1 or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.9 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.10 INTERIM ANALYSES

6.10.1 Planned Interim Analyses

Primary Endpoint of Progression-Free Survival

There is no planned interim analysis of the primary endpoint of PFS.

Primary Endpoint of Overall Survival

A total of three analyses of OS will be performed, including two interim analyses and one final analysis. The boundary for statistical significance at each OS analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming (OBF) function (Lan and DeMets 1983) to maintain the overall type I error rate (Hung et al. 2007; Glimm et al. 2009) at either 0.03 or 0.05 level, depending on whether primary endpoint of PFS is significant at 0.02 level. The OBF boundary for statistical significance is provided in Table 12. The OS endpoint will be considered positive in the ITT population if statistical significance is achieved in favor of the experimental arm for any of the two OS interim analyses or the final analysis.

Table 12 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Hazard Ratios

	OS Interim Analysis 1	OS Interim Analysis 2	Final OS
Percent Information	53% 175 events	80% 260 events	100% 325 events
Timing (from FPI)	27 months (PFS primary)	39 months	52 months
OBF Boundary when $\alpha = 0.03$ (0.05)	0.0019 (0.0045)	0.0125 (0.0231)	0.0259 (0.0424)
MDD when $\alpha = 0.03$ (0.05)	HR $\leq$ 0.62 (HR $\leq$ 0.65)	HR $\leq$ 0.73 (HR $\leq$ 0.75)	HR $\leq$ 0.78 (HR $\leq$ 0.80)

FPI = first patient in; HR = hazard ratio; MDD = minimum detectable difference; OBF = O'Brien-Fleming; OS = overall survival; PFS = progression-free survival.

The first interim analysis of OS will be performed at the time of the PFS primary analysis. A total of 175 OS events are expected at the first interim analysis of OS, which corresponds to 53% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p < 0.0019$. If there are significantly fewer (< 160) OS events than the expected 175 OS events, then the first interim analysis will be delayed until 175 OS events occur. An administrative α of 0.000001 (negligible impact on overall type I error rate) will be spent on the OS hypothesis at the time of the planned PFS.

The second interim analysis of OS will be performed when approximately 260 deaths have occurred, which corresponds to approximately 80% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p < 0.0125$.

The final analysis of OS will be performed when 325 deaths (65% of 500 patients in the ITT population) have occurred. Statistical significance will be declared if $p < 0.0259$ when exactly 325 deaths have occurred at the time of the final OS analysis.

The actual OBF boundary will be calculated at time of analysis based on actual number of events observed.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

Electronic Case Report Forms and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Patient-reported outcome data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. Electronic Case Report Forms will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. Electronic Case Report Forms should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of

the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants may be submitted to government or other health research databases or shared with researchers, government

agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted CSRs and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations

from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 140–180 sites globally will participate to randomize approximately 500 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will monitor and evaluate patient safety until the primary PFS analysis throughout the study. Tumor response and progression will be evaluated by an IRF.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted CSRs and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country,

the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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 accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Activities

Assessment Window (Days) [a]	Screening [b]		Treatment Cycles (21-day cycles)	Treatment Discontinuation	Follow-Up (±1 month)
	Days –28 to –1	Days –14 to –1	Day 1 (±3 days)	≤30 Days after Final Dose	
Informed consent	x [c]				
Tumor tissue specimens [d]	x				
Demographic data	x				
Medical history, including cancer and RCC history, and baseline conditions	x				
Patient-reported outcome [e]			x	x	x [f, g]
Vital signs [h]	x		x	x	
C-reactive protein	x				
Weight	x		x	x	
Height	x				
Complete physical examination [i]	x			x	
Limited physical examination [j]			x [k]		
Karnofsky Performance Status	x		x [k]	x	
ECG (12-lead)/ Echocardiogram [l]		x [l]	x	x	
Hematology [m]		x	x [k]	x	
Chemistry [n]		x	x [k]	x	
Pregnancy test [o]		x	x [k]	x	
Coagulation (INR, aPTT)		x		x	
TSH, free T3 (or total T3), free T4 [p]	x		x	x	
Viral serology [q]	x				

Appendix 1: Schedule of Activities (cont.)

Assessment Window (Days) [a]	Screening [b]		Treatment Cycles (21-day cycles)	Treatment Discontinuation	Follow-Up (±1 month)
	Days –28 to –1	Days –14 to –1	Day 1 (±3 days)	≤30 Days after Final Dose	
Urinalysis [r, s]		x	x [k]		
UPCR		x	x [k, t]		
PK samples			See Appendix 2		
ADA samples			See Appendix 2		
Blood sample for biomarkers (central laboratory)			See Appendix 2		
Urine sample for biomarkers (central laboratory)			*See Appendix 2*		
Blood sample for RBR (optional) [u]			x		
Tumor biopsy, if clinically feasible			At time of radiographic progression [v]		
Tumor tissue biopsy at other timepoints (optional) [w]			Any time during study treatment, observation FU or survival FU (at investigator's discretion)		
Tumor response assessments	x [x]		x [y, z]		
Concomitant medications [aa]		x	x	x	
Adverse events [bb]	x		x	x	x
Atezolizumab administration			x [cc]		
Cabozantinib dispensing/reconciliation			x [dd]		
Survival follow-up and anti-cancer treatment					x [ee]

ADA = anti-drug antibody; CRP = C-reactive protein; CT = computed tomography; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FKSI-19 = Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NA = not applicable; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire–Core 30 Questionnaire; RBR = Research Biosample Repository; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TSH = thyroid-stimulating hormone; UPCR = Urine Protein/Creatinine ratio.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] The first dosing day (Day 1 of Cycle 1) should occur within 3 days from the date of randomization.

[b] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. If re-screening is required, then HBV, HCV, HIV, and CRP from the initial screening may be acceptable for screening assessment if performed < 60 days from Day 1 of Cycle 1.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[d] Representative archival tumor tissue sample and, if clinically feasible, a fresh tumor sample obtained at baseline for exploratory research on biomarkers (e.g., PD-L1 status via central testing), including biomarker assay development. See Section 4.5.7 for tissue sample requirements.

[e] Patient-reported outcome assessments (EORTC QLQ-C30, FKSI-19, and EQ-5D-5L questionnaires) will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments that could bias patient's rating and the administration of study treatment. Study personnel should confirm all questionnaires for completeness before the patient leaves the investigational site. Patient-reported outcome instruments will be completed by patients on Day 1 of each cycle for the first 12 cycles and then on Day 1 of every other cycle during study treatment, and at the end-of-treatment visit. For PROs after treatment discontinuation, please see footnotes [f] and [g].

[f] Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the questionnaires (EORTC QLQ-C30, FKSI–19, and EQ-5D-5L) at the end-of-treatment visit and then until disease progression when going to the clinic for any study-related assessments.

[g] All patients will complete the EORTC QLQ-C30, FKSI–19 and EQ-5D-5L questionnaires at 4 subsequent survival follow- up visits (i.e., at 3, 6, 9, and 12 months after radiographic disease progression per RECIST v1.1) or, for patients who continue atezolizumab after radiographic disease progression, loss of clinical benefit as determined by the investigator. Survival follow-up assessments may be conducted over the telephone.

[h] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (±10) minutes after the infusion.

[i] The complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints.

[k] If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated. At all cycles subsequent to Day 1 of Cycle 1, Karnofsky Performance Status and limited physical examination must be performed within 96 hours prior to study treatment administration.

[l] 12-lead ECG recordings will be obtained during screening (within 14 days prior to initiation of study treatment), on Day 1 of Cycle 1 (predose), on Day 1 of Cycle 2, on Day 1 of Cycle 3, and every 4 cycles thereafter (i.e., Day 1 of Cycle 7, Day 1 of Cycle 11, and so on) and at the end-of-treatment visit. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. Electrocardiograms will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of LVEF (echocardiogram) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease, and/or other arterial thromboembolic disease. If no clinical symptoms were present at screening, ECG does not need to be repeated on Day 1 of Cycle 1.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, urate, ALP, ALT, AST, and LDH.

[o] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed at every cycle (predose) during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1 and every 4 cycles thereafter (i.e., Cycles 5, 9, 13, and so on).

[q] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Urinalysis should be performed at screening and every 3 weeks or as clinically indicated during study treatment.

[t] UPCR should be performed at screening*, Cycle 1 (not repeated if screening UPCR is performed within 72 hours of Day 1 of Cycle 1, please see footnote [k]), Cycle 3, and* every other cycle (i.e., every 6 weeks) *thereafter* during study treatment or more frequently as clinically indicated.

[u] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. The RBR blood sample can be accepted *on* Day 1 of Cycle 1 *and anytime thereafter* and should only be collected at one timepoint during the study.

[v] Patients will undergo a tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.7 for tissue sample requirements and Section 4.5.11 for biopsy in relation to cabozantinib dosing.

[w] Optional tumor tissue biopsies are to be performed only for patients at participating sites who have provided written informed consent to participate. Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.7 for details. See Appendix 2 for schedule. See Section 4.5.11 for instructions on cabozantinib dosing for patients undergoing biopsy.

[x] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed, and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At subsequent (post-screening) tumor assessments, patients with a history of irradiation brain metastasis at screening are not required to undergo brain scan unless clinically indicated. The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used to assess disease sites at screening should be used for subsequent tumor assessments. Bone scans and CT scans of the neck should also be performed at baseline, if clinically indicated.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[y] Patients will undergo tumor assessments at baseline, every 9 weeks (±7 days) for the first 18 months following treatment initiation, and every 12 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue study treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. All patients, regardless of arm, will also undergo a follow-up post-disease progression tumor assessment after investigator assessment of radiographic disease progression per RECIST v1.1. When feasible, this subsequent scan will take place on the same schedule as prior to progression at 9 weeks (±7 days) if disease progression occurred in the first 18 months, and at 12 weeks (±7 days) if disease progression occurred after the first 18 months following treatment initiation.

[z] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until the end of the special reporting period defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[cc] The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[dd] Cabozantinib tablets will be given on Day 1 of Cycle 1 after atezolizumab infusion. On Day 1 of Cycle 1, the patient will fast (with the exception of water) for at least 2 hours before receiving cabozantinib. Upon completion of the 2-hours fast, the patient will receive the oral dose of cabozantinib with a minimum of 8 oz (240 mL) of water in the clinic and then the patient will continue to fast for 1 hour. Patients will take tablets once daily at home thereafter until study treatment is discontinued. Tablets should be taken at approximately the same time QD, preferentially before going to bed, and should adhere to the fasting requirements described in Section 4.3.2.2.

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±1 month) until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only where allowed per local regulations.

Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type in Each Arm	
		Atezolizumab + Cabozantinib	**Cabozantinib**
Screening	NA	• Archival biopsy • Fresh biopsy	• Archival biopsy • Fresh biopsy
Day 1 of Cycle 1	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum, *urine*) • RBR (blood) [a]	• Biomarker (PBMC, plasma, serum, *urine*) • RBR (blood) [a]
	30 (±10) minutes after end of *atezolizumab* infusion	• Atezolizumab PK (serum)	–
Day 1 of Cycle 2	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Cabozantinib PK (plasma) • Biomarker (PBMC, plasma, serum, *urine*)	• Biomarker (PBMC, plasma, serum, *urine*) • Cabozantinib PK (plasma)
Day 1 of Cycles 3 and 4	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Cabozantinib PK (plasma) • Biomarker (*PBMC*, plasma, serum, *urine*)	• Biomarker (*PBMC*, plasma, serum, *urine*) • Cabozantinib PK (plasma)
Day 1 of Cycles 8, 12 and 16	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)	–
At timing of fresh biopsy (during treatment or at progression)	At visit	• Biomarker (PBMC, plasma, serum, *urine*) [b]	• Biomarker (PBMC, plasma, serum, *urine*) [b]

Appendix 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Visit	Timepoint	Sample Type in Each Arm	
		Atezolizumab + Cabozantinib	**Cabozantinib**
Treatment discontinuation visit (≤ 30 days after final dose)	NA	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Cabozantinib PK (plasma) • Biomarker (PBMC, plasma, serum, *urine*)	• Biomarker (PBMC, plasma, serum, *urine*) • Cabozantinib PK (plasma)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; NA = not applicable; PK = pharmacokinetic; RBR = Research Biosample Repository

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. The RBR blood sample can be accepted at Cycle 1, Day 1 *and anytime thereafter*, and should only be collected at one timepoint during the study.

[b] Blood *and urine* collections should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. If the progression visit is at the same time as the treatment discontinuation visit, only one set of biomarker samples needs to be collected.

Appendix 3 Response Evaluation Criteria in Solid Tumors, (RECIST) Version 1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of 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 measurable lesions if the soft-tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed with use of calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

Computed tomography is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should 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.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF; e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response (CR) criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions that Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- CR: Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for disease progression

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-disease progression: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Disease progression: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will; therefore, be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare disease progression for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall disease progression at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the

very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore, non-target) disease only, Table 2 is to be used.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-DP	No	PR
CR	Not all evaluated	No	PR
PR	Non-DP or not all evaluated	No	PR
SD	Non-DP or not all evaluated	No	SD
Not all evaluated	Non-DP	No	NE
PD	Any	Yes or no	DP
Any	DP	Yes or no	DP
Any	Any	Yes	DP

CR = complete response; DP = disease progression; NE = not evaluable; PR = partial response; SD = stable disease.

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-DP	No	Non-CR/non-DP [a]
Not all evaluated	No	NE
Unequivocal DP	Yes or no	DP
Any	Yes	DP

CR = complete response; DP = disease progression; NE = not evaluable.

[a] "Non-CR/non-DP" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of disease progression. For example, if a patient had a baseline

sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved disease progression status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.
The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 and Table 2.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 4 Modified RECIST for Immune-Based Therapeutics (iRECIST) v1.1

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009) have been developed to allow for unconventional response and progression patterns. These include modified RECIST for immune-based therapeutics (iRECIST; Seymour et al. 2017) v1.1, which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 convention will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the eCRF but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

Immune-modified RECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions, as described in Section 3.1.

EVALUATION OF LESIONS TO SUPPORT iRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST v1.1

Immune-modified RECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. Response Evaluation Criteria in Solid Tumors v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions (see Appendix 3) also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (disease progression), or "present without unequivocal progression" (non-CR/non-disease progression), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as disease progression at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short

axis of a lymph node is <10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to <15 mm (or even <10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (disease progression), or present without unequivocal progression (non-CR/non-disease progression), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as disease progression at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1 • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints • Up to a maximum of five measurable new lesions total (with a maximum of one lesion per organ) should be selected and measured at each timepoint • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint

CR = complete response; iRECIST = modified RECIST for immune-based therapeutics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

Appendix 5 European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30)

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 6 EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

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English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

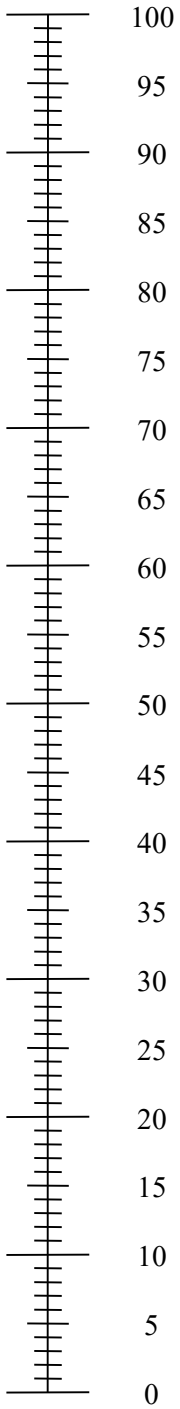
PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



Appendix 7 Functional Assessment of Cancer Therapy-Kidney Symptom Index 19

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NCCN-FACT FKSI-19 (Version 2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
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Appendix 8 Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). *Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.* Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix 9 Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 10 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely • Re-evaluate on serial imaging • Consider patient referral to pulmonary specialist
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL • 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] • For recurrent events, treat as a Grade 3 or 4 event
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Bronchoscopy or BAL is recommended • 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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients eligible *for study treatment* must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab • Monitor LFTs until values resolve to within normal limits or to baseline values
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset [a] • Initiate treatment with 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]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. c • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • 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.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein,

platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3–5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab • Initiate symptomatic treatment • Endoscopy is recommended if symptoms persist for >7 days • Monitor closely
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Initiate symptomatic treatment • Patient referral to GI specialist is recommended • For recurrent events or events that persist >5 days, 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]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event 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]

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

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 4.

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

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly
Symptomatic hypothyroidism	• Withhold atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly • Consider patient referral to endocrinologist • Resume atezolizumab when symptoms are controlled, and thyroid function is improving
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab • Monitor TSH every 4 weeks **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism
Symptomatic hyperthyroidism	• Withhold atezolizumab • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider patient referral to endocrinologist • Resume atezolizumab when symptoms are controlled, and thyroid function is improving • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to endocrinologist • Perform appropriate imaging • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia Grade 3 or 4	• Withhold atezolizumab • Initiate treatment with insulin • Monitor for glucose control • Resume atezolizumab when symptoms resolve, and glucose levels are stable
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to endocrinologist • Perform brain MRI (pituitary protocol) • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • Initiate hormone replacement if clinically indicated • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • For recurrent hypophysitis, treat as a Grade 4 event
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to endocrinologist • Perform brain MRI (pituitary protocol) • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • Initiate hormone replacement if clinically indicated

MRI = magnetic resonance imaging.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If 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]

Table 6 Management Guidelines for Immune-Mediated Myocarditis (cont.)

Event	Management
Immune-mediated myocarditis, Grade 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

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

Infusion-related reactions 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.

Cytokine release syndrome 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). Cytokine release syndrome 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.

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 medical management of IRRs and CRS are provided in Table 7.

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.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion • Upon symptom resolution, wait for 30 minutes and then restart infusion at rate to 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

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
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 (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Consider anti-cytokine therapy [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 Medical Monitor. • 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 Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
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 Medical Monitor [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 (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Consider anti-cytokine therapy [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 Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, Bi-PAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor [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 (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Consider anti-cytokine therapy. [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 Medical Monitor. • Hospitalize patient until complete resolution of symptoms

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

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. Nation Cancer Institute Common Terminology Criteria for Adverse Events v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq 38°C$ 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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. 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 consulting the Medical Monitor and considering the benefit–risk ratio.

[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

PANCREATIC EVENTS

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 workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab • Monitor amylase and lipase weekly • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to GI specialist • Monitor amylase and lipase every other day • If no improvement, consider treatment with 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] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor [c]

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

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

GI = gastrointestinal; ULN = upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

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

Table 9 Management Guidelines for Dermatologic Events

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

Table 9 Management Guidelines for Dermatologic Events (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

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 workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab • Investigate etiology
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Investigate etiology • Initiate treatment as per institutional guidelines • 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]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Initiate treatment as per institutional guidelines
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to neurologist • Initiate treatment as per institutional guidelines • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone

Table 10 Management Guidelines for Neurologic Disorders (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated 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.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to renal specialist • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab 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 (i.e., > 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 agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated 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 among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab • Refer patient to rheumatologist or neurologist • Initiate treatment as per institutional guidelines
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor • Refer patient to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or 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 Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019)* • 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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 11 Risks Associated with Cabozantinib and Guidelines for Management of Adverse Events Associated with Cabozantinib

This appendix provides guidelines for management of patients who experience cabozantinib-associated adverse events (e.g., GI disorders, hemorrhage, thromboembolic events, hypertension, osteonecrosis, proteinuria, hepatocellular toxicity, blood system disorders, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders).

DOSE MODIFICATIONS

For information on dose modification, see Section 5.1.3.1.

TREATMENT INTERRUPTION

For information on treatment interruption, see Section 5.1.3.2.

MANAGEMENT GUIDELINES

The most frequent adverse events experienced by ≥20% of patients treated with cabozantinib in descending order of frequency were diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, palmar-plantar erythrodysesthesia (PPE), constipation, hypertension, dysgeusia, dysphonia, and asthenia. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator Brochure.

Other medically important but less frequent adverse events include arterial thrombotic adverse events (e.g., transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic adverse events (e.g., deep venous thrombosis [DVT] and pulmonary embolism [PE]), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses, including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; preferred term: posterior reversible encephalopathy syndrome [PRES]).

Adverse events associated with laboratory test abnormalities that were experienced by ≥5% of cabozantinib-treated patients 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 (see Section 5.1.3).

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

GASTROINTESTINAL DISORDERS

Gastrointestinal (GI) perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, patients 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 2016) are present. Discontinue cabozantinib and initiate appropriate management in patients who have been diagnosed with GI perforation or fistula.

Diarrhea: Patients 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 1. Administration of anti-diarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some patients may require concomitant treatment with more than one anti-diarrheal agent. When therapy with anti-diarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, re-treatment 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 1 Management of Diarrhea Associated with Cabozantinib

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

Nausea and vomiting: Anti-emetic 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. Anti-emetic medications should be assessed for potential drug interactions (see Section 4.4 for further details).

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 patients undergoing treatment with VEGF pathway inhibitors.

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

HEMORRHAGE

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Patients should be monitored for bleeding events with serial complete blood counts and physical examination while in the study. The risk of hemorrhage in cabozantinib-treated patients with brain metastases has not been thoroughly analyzed. Patients 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 patients with serious and life-threatening bleeding events or recent hemoptysis ($\geq$2.5 mL of red blood).

THROMBOEMBOLIC EVENTS

Thromboembolic events are frequent in cancer patients due to procoagulant changes induced by the malignancy or anti-cancer therapy. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib, including fatal events. Patients who develop a PE and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in patients with PE or DVT if it is determined that the event is uncomplicated and that the patient 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 the discretion of the investigator and according to individual protocols. Low-molecular weight heparin (LMWH) or anticoagulation with direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban is allowed for the treatment of thromboembolic events if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
Note: Anticoagulation with the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor betrixaban is not allowed. See Sections 4.4.1 and 4.4.6 for detailed information regarding the use of anticoagulants.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in patients

who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

HYPERTENSION

Table 2 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure (BP) 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 patients with hypertensive emergency.

Table 2 Management of Hypertension 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 patient is symptomatic interrupt cabozantinib treatment
≥160 mm Hg (systolic) OR ≥110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor patient 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. • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥160 mmHg) are sustained and not adequately manageable or if systolic BP is >180 mmHg or sustained diastolic BP>110 mm Hg, or if patient is symptomatic • Restart cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
	and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic

Table 2 Management of Hypertension Associated with Cabozantinib (cont.)

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Hypertensive emergency [b]	• Discontinue cabozantinib treatment

BP = blood pressure.

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

[b] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

STOMATITIS AND MUCOSITIS

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

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

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

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

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysesthesia (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 patients in the 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 3.

Table 3 Management of Hand-Foot Syndrome Associated with Cabozantinib

NCI 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. [a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume cabozantinib at a reduced dose if PPE recovers to Grade $\leq$ 1. Discontinue the patient from study treatment if PPE does not improve within 6 weeks.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug; PPE = palmar-plantar erythrodysesthesia.

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

OSTEONECROSIS

Osteonecrosis has been reported in patients 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 patients regarding oral hygiene practice and to quickly report symptoms to the investigator. Caution should be used in patients receiving bisphosphonates.

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

PROTEINURIA

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring urine protein-to-creatinine ratio (UPCR). Table 4 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in patients 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 4 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-hour protein assessment within 7 days • No change in cabozantinib treatment required if UPCR≤2 mg/mg or urine protein≤2 g/24 hours on 24-hour urine collection • Reduce dose or interrupt cabozantinib treatment if UPCR>2 mg/mg on repeat UPCR testing or urine protein>2 g/24 hours on 24-hour 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 the Sponsor. • If UPCR >2 mg/mg, repeat UPCR monitoring within 7 days and once per week. If UPCR <2 mg/mg on two consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading).
≥3.5 mg/mg (≥395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR monitoring within 7 days and/or 24-hour 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-to-creatinine ratio.

NERVOUS SYSTEM DISORDERS

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

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

HEPATOCELLULAR TOXICITY

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

Management guidelines for hepatotoxicity related to cabozantinib treatment are provided in Table 5.

Table 5 Management of Hepatotoxicity Associated with Cabozantinib

Severity of Transaminase (ALT or AST) Elevations by NCI CTCAE	Treatment/Cabozantinib Dose Modification
Grade 1	• Dose adjustment is usually not required • Consider discontinuing concomitant hepatotoxic medications and adding supportive care as indicated
Grade 2	• Interrupt cabozantinib • Restart cabozantinib, at the same dose or a reduced dose at investigator discretion, after laboratory abnormalities have resolved to no higher than NCI CTCAE Grade ≤ 1 or baseline grade
Grade ≥ 3	• Interrupt cabozantinib and consider more frequent monitoring of ALT and/or AST • Restart cabozantinib at a reduced dose after laboratory abnormalities have resolved to NCI CTCAE Grade ≤ 1 or baseline grade • Discontinue if laboratory abnormalities cannot be reversed despite interruption of cabozantinib

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

The following conditions require discontinuation of cabozantinib unless these laboratory abnormalities have recovered to Grade 1 or baseline grade after an interruption and the Sponsor has approved reinstitution of cabozantinib:

- Drug-related ALT or AST $> 8 \times$ upper limit of normal (ULN)
- Drug-related ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN without reasonable other explanation, consistent with drug-induced liver injury

INFECTIONS AND INFESTATIONS

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be

managed with dose interruptions and/or dose reductions. Patients 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. However, for patients with thrombocytopenia dose modifications should be followed in accordance with Table 9 in Section 5.1.3.1. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

FATIGUE

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

WEIGHT LOSS

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

CORRECTED QT PROLONGATION

The effect of orally administered cabozantinib 140 mg once a day (QD) on corrected QT interval (QTc) was evaluated in a placebo-controlled study in patients with medullary thyroid cancer. A mean increase in QT interval corrected with use of Fridericia's formula (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 patients in this study had a QTcF $>$480 ms. Review of the larger safety database (approximately 5000 patients exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong CYP450 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time in the study there is an increase in QTcF to an absolute value $>$480 ms or an increase of $>$60 ms above baseline per the site's ECG read, 2 additional ECGs must be performed with intervals not less than 3 minutes apart within 30 minutes after the initial ECG.

If the average QTcF from the 3 ECGs is $>$480 ms or the average increase is $>$60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic patients (e.g., 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 patients for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (https://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is $\leq$480 ms and the average increase is $\leq$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

Patients 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 $>$480 ms or increase of $>$60 ms above baseline is not confirmed by local cardiologist
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to $\leq$480 ms or increase of $\leq$60 ms above baseline
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

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

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 re-initiation of study treatment is at a reduced dose

ELECTROLYTE DISORDERS

Serum electrolyte imbalance, including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia has been reported during treatment with cabozantinib. There are many causes for an electrolyte imbalance, including loss of body fluids (e.g., from prolonged vomiting or diarrhea), inadequate diet, kidney disease, and use of certain concomitant medications (e.g., diuretics). Electrolyte imbalance may create a variety of symptoms (e.g., weakness, fatigue, confusion, muscle spasm, constipation, and irregular heartbeat). Serum electrolyte levels should be monitored closely while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines (see Section 5.1.3.1, Table 9) and may include oral or IV replacement.

ENDOCRINE DISORDERS

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

RESPIRATORY DISORDERS

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

Appendix 12 International Metastatic Renal Cell Carcinoma Database Consortium Risk Factors

Prognostic factors:

- Less than 1 year from time of diagnosis to systemic therapy
- Karnofsky Performance Status $< 80\%$
- Hemoglobin $<$ lower limit of normal (ULN; normal: 120 g/L or 12 g/dL)
- Corrected calcium $>$ upper limit of normal (normal: 8.5–10.2 mg/dL)
- Neutrophils $>$ ULN (normal: $2.0–7.0 \times 10^9$/L)
- Platelets $>$ ULN (normal: 150,000–400,000)

Risk groups:

- Favorable Risk: If patient has 0 factors
- Intermediate Risk: If patient has 1–2 factor(s)
- $Poor$ Risk: If patient has 3–6 factors

Suggested corrected calcium formula:

$$\text{Corrected calcium} = [0.8 \times (\text{normal albumin} - \text{patient's albumin})] + \text{serum calcium}$$

Appendix 13 Definition of Sarcomatoid Renal Cell Carcinoma: Stanford Surgical Pathology Criteria

SARCOMATOID RENAL CELL CARCINOMA

Definition

Renal cell carcinoma (RCC) of any type exhibiting at least focal sarcomatoid/spindle cell differentiation.

Diagnostic Criteria

- Represents a form of high-grade transformation, not a distinct subtype of RCC
- May occur in any of the standard subtypes of RCC
- Reported to occur in 5–8% of RCCs

  Less common in our experience.
- Should not be reported as the subtype of RCC

Requires Evidence of Epithelial Differentiation

- Concurrent areas of RCC of any type, OR
- Immunohistochemical positivity for keratin or EMA

  (Keratin and EMA expression may be appropriate for some sarcomas, including leiomyosarcomas).

Requires a Spindle Cell Component Measuring at Least 1 Low-Power (40×) Field

- May be discrete or intermixed with epithelial elements
- May be very focal

Most Common Patterns are Fibrosarcoma and Malignant Fibrous Histiocytoma

- Rare cases reported with patterns of rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and hemangiopericytoma
- Pattern does not appear to affect prognosis

Grade of Sarcoma is Not Clinically Significant

- May range from low to high

  Based on cellularity, atypia, mitotic figures.

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