CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Open-Label, Controlled Study of Cabozantinib (XL184) in Combination with Atezolizumab vs Second Novel Hormonal Therapy (NHT) in Subjects with Metastatic Castration-Resistant Prostate Cancer

PROTOCOL NUMBER:	XL184-315
STUDY TREATMENT:	Cabozantinib (XL184) in Combination with Atezolizumab vs Second NHT
IND NUMBER:	144,735
EudraCT NUMBER:	2020-000348-77
SPONSOR:	Exelixis, Inc. 1851 Harbor Bay Parkway Alameda, CA 94502
MEDICAL MONITOR:	PPD
DATE FINAL (Version 0.0):	20 December 2019
DATE AMENDED:	24 April 2020 **PROTOCOL AMENDMENT 1.0**
	13 May 2021 **PROTOCOL AMENDMENT 2.0**
	02 June 2022 **PROTOCOL AMENDMENT 3.0**
	10 Nov 2022 **PROTOCOL AMENDMENT 4.0**
	24 Jan 2023 **PROTOCOL AMENDMENT 5.0**

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PROTOCOL APPROVAL PAGE

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Approval of protocol by Sponsor:

PPD

PPD Date

(on behalf of PPD

PROTOCOL ACCEPTANCE FORM

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

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Phase 3, Randomized, Open-Label, Controlled Study of Cabozantinib (XL184) in Combination with Atezolizumab vs Second Novel Hormonal Therapy (NHT) in Subjects with Metastatic Castration-Resistant Prostate Cancer

PROTOCOL NUMBER

XL184-315

CLINICAL PHASE

Phase 3

RATIONALE

In 2018, prostate cancer was the fourth most commonly diagnosed malignancy worldwide behind cancers of the lung, breast, and colorectum (GLOBOCAN 2018). Incident prostate cancer was reported in 1.3 million men and accounted for 7.1% of all new cancer diagnoses that year. It is the most common cancer among men worldwide and the second leading cause of cancer deaths in the US (Bashir 2015), where its incidence in 2018 exceeded that of cancers of the bladder, kidney, and testis combined (NIH NCI SEER 2018).

There are multiple histologic types of prostate cancer, but adenocarcinoma accounts for the vast majority of cases. Prostate adenocarcinoma typically is associated with elevation in the serum prostate-specific antigen (PSA) and often responds to testosterone-lowering (castration) and other hormonal manipulations targeting signaling through the androgen receptor (AR) axis.

Prostate adenocarcinoma is radiographically localized at diagnosis in the majority of cases where PSA testing is widely implemented. Approximately two-thirds of men with radiographically localized disease are cured with definitive localized therapy (radical prostatectomy or radiotherapy), but the remainder will experience recurrence heralded by a rising PSA, local radiographic occurrence, and/or metastases. Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced or metastatic prostate cancer due to the androgen dependency of this disease. A rising PSA without radiographically evident metastases despite initiation of ADT castration signifies a non-metastatic castration-resistant state (non-metastatic castration-resistant prostate cancer [M0 CRPC]). De novo metastatic disease (metastatic castration-sensitive prostate cancer [mCSPC]) accounts for 3-7% of new cases of prostate cancer in developed nations and its incidence in the US may be rising due to recent declines in population-based PSA surveillance (Weiner et al 2016). Furthermore, de novo metastatic disease is commonly diagnosed in countries where PSA testing is not part of standard clinical practice. M0 CRPC and mCSPC are the primary pathways to metastatic castration-resistant prostate cancer (mCRPC), which all subjects enrolling in this Phase 3 study are required to have.

Systemic treatment alternatives for patients with mCRPC now include chemotherapy, immunotherapy, androgen signaling pathway receptor inhibitors, radionuclide therapy, and PARP inhibitors (Tannock et al 2004, de Bono et al 2010, de Bono et al 2011, Kantoff et al 2010, Parker

et al 2013, Ryan et al 2015, Scher et al 2012, Beer et al 2014, Beer et al 2017, de Bono et al 2020, Abida et al 2020; Sartor et al 2021).

ADT has historically been used to treat mCSPC preceded by radiographically localized disease. However, docetaxel/prednisone and NHTs, including abiraterone, apalutamide, and enzalutamide have been shown to improve outcomes when combined with ADT initiation (Sweeney et al 2015, Kyriakopolous et al 2018, James et al 2016, Fizazi et al 2017, Fizazi et al [Lancet Oncol] 2019, Armstrong et al 2019, Chi et al 2019).

For M0 CRPC patients, three AR antagonists (apalutamide, enzalutamide, and darolutamide) have demonstrated improvements in metastasis-free survival (MFS) and overall survival (OS) compared with placebo in men with a PSA doubling time less than 10 months (Smith et al 2018, Hussain et al 2018, Fizazi et al [NEJM] 2019, Sternberg et al 2020, Fizazi et al 2020, Smith et al 2021).

Potentially linked to the recent introduction of new treatments earlier in disease, the incidence of visceral metastases in men with mCRPC may be increasing and is associated with a particularly poor prognosis, particularly in the setting of liver disease (Nafissi et al 2019, Iwamoto et al 2018, Pezaro et al 2014, Whitney et al 2017).

Standard-of-care therapies used for patients with visceral disease include taxane-based chemotherapy and NHTs (NCCN [Prostate Cancer v2.2019] 2019). However, none of these treatments is likely curative, and, upon progression, many patients with mCRPC will likely have already been treated with an NHT either as their first treatment for mCRPC or earlier disease (mCSPC or M0 CRPC), respectively.

Cabozantinib (XL184) is a potent, orally bioavailable inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization, including the vascular endothelial growth factor receptor (VEGFR2), MET, RET, and KIT. Somatic KIT mutations have been associated with aggressive forms of prostate cancer (Martinez-Gonzalez et al 2018). Increased expression of MET, HGF (the ligand for MET), and VEGF have been observed in prostate carcinomas and are associated with poorer prognosis (Knudsen et al 2002, Zhang et al 2010, Humphrey et al 2006, Bok et al 2001, George et al 2001). Cabozantinib targets also include TYRO3, AXL, and MER (TAM family kinases) and are implicated in promoting suppression of an antitumor immune response.

Cabozantinib tablets (60 mg) are approved in the United States, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx® US Prescribing Information [PI] and European Medicines Agency [EMA] Summary of Product Characteristics [SmPC]). Cabozantinib tablets have also been approved in the US and other regions for the treatment of hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib and in the US for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible (HCC: 60 mg; DTC: 40 mg [in pediatric patients $\geq$ 12 years with body surface area (BSA) < 1.2 m^2] and 60 mg [in adult and pediatric patients $\geq$ 12 years with BSA $\geq$ 1.2 m^2]; Cabometyx US PI and EMA SmPC). The EU has also approved cabozantinib for similar use in adults but not in pediatric patients. Cabozantinib tablets (40 mg) are also approved for advanced RCC as a first-line treatment in combination with nivolumab.

Cabozantinib capsules (140 mg) are approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq® US PI and EMA SmPC). The capsule and tablet formulations are not bioequivalent or interchangeable.

COMET-1 was a randomized, double-blind, controlled Phase 3 study of cabozantinib (60 mg orally [po] once daily [qd]) vs prednisone (5 mg po twice a day [bid]) in 1028 men with bone-metastatic CRPC who had previously been treated with docetaxel and at least one NHT (abiraterone acetate ["abiraterone"] with prednisone, and/or enzalutamide; Smith et al 2016). This trial enrolled subjects in third- or later-line mCRPC where no therapy has yet proved efficacious. Cabozantinib did not demonstrate a statistically significantly improvement in the primary endpoint, OS, although there was a positive trend. Median radiographic progression-free survival (PFS) per Investigator (including bone scan progression) was improved in the cabozantinib group (5.6 vs 2.8 months; hazard ratio [HR] 0.48 [95% confidence interval {CI}: 0.40, 0.57; stratified logrank p-value < 0.0001]), and improvements were also observed in circulating tumor cell (CTC) conversion (which has been associated with OS; Scher et al 2012), bone biomarkers, and time to symptomatic skeletal event (SSE) incidence. Notably, OS and PFS (based on computerized tomography [CT]/ magnetic resonance imaging [MRI] with or without bone scan assessments) benefits among those who received cabozantinib were observed in a post hoc subgroup analysis of those with visceral disease, which suggests a potential role for cabozantinib in the treatment of such mCRPC.

Immune checkpoint inhibitor (ICI) monotherapy with the PD-1 inhibitor, pembrolizumab; the PD-L1 inhibitor, atezolizumab; and the CTLA-4 inhibitor, ipilimumab; as well as the combination of the PD-1 inhibitor, nivolumab, with ipilimumab have been studied in mCRPC. Prostate cancer is often a slow-growing tumor that may allow enough time for ICI therapy to activate the immune system with higher percentages of regulatory T-cells (Tregs) being found in higher stages of prostate cancer and tumor-infiltrating cytotoxic lymphocytes expressing high levels of PD-1 (an indicator of T-cell exhaustion), among other observations (Schepisi et al 2017, Ebelt et al 2009, Sfanos et al 2009). However, the limited data available from ICI monotherapy trials in patients with mCRPC suggest that single-agent immunotherapy may only benefit a modest subset of patients with mCPRC (Kim et al 2018, Kwon et al 2014, Sharma et al 2019).

Preclinical studies (Kwilas et al 2014, Lu et al 2017, Wang et al 2019) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment, which might lead to synergistic effects from combination treatment with ICIs, independent of PD-L1 expression.

COSMIC-021 is an ongoing Phase 1b study that evaluates the efficacy of cabozantinib in combination with atezolizumab in multiple tumor types including subjects with metastatic CRPC without small-cell features who have radiographically progressed in soft tissue on or after NHT (enzalutamide and/or abiraterone) initiated for treatment of metastatic disease. Subjects are required to have measurable soft tissue (visceral or adenopathic) disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Prior treatment with docetaxel is only permitted when given in combination with ADT for metastatic castration-sensitive prostate cancer prior to treatment with NHT. Subjects receive cabozantinib 40 mg po qd and atezolizumab 1200 mg intravenously [IV] every 3 weeks [q3W]. As of 21 October 2019, 61 CRPC subjects had

been enrolled in this study and 44 of these subjects with at least 12 weeks of follow-up were evaluable for response. Fourteen of the 44 evaluable subjects (31.8%) had a confirmed tumor response per RECIST 1.1 by Investigator assessment, including 2 subjects with a complete response and 12 with partial response. Disease control rate was 80%. An additional subject, not included as responder above, with initial PD per RECIST 1.1 exhibited a durable irPR per irRECIST criteria. An objective tumor response rate was also observed (33%) in 36 patients with features of disease associated with poor prognosis: measurable visceral disease and/or measurable extrapelvic lymph node metastasis. The observed clinical activity of the combination therapy in COSMIC-021 is especially encouraging given the more limited single-agent activity of either cabozantinib or atezolizumab in subjects with metastatic CRPC and is suggestive of cooperative effects of these agents (Schoffski et al 2017, Kim et al 2018). For further information on COSMIC-021, refer to the current cabozantinib Investigator's Brochure.

There is a significant unmet medical need for treatment options for men with mCRPC who have previously received an NHT for mCRPC and/or earlier lines of disease (mCSPC, M0 CRPC) and who have measurable visceral disease or measurable extrapelvic adenopathy. Based on the encouraging data from Cohort 6 of Study XL184-021 (COSMIC-021), this Phase 3 study will evaluate the safety and efficacy of cabozantinib in combination with atezolizumab versus a second NHT in subjects with such mCRPC. This study is particularly suited to men with a good performance status who wish to avoid chemotherapy or to men deemed unable to tolerate side effects from chemotherapy.

OBJECTIVES and ENDPOINTS

The primary objective of this study is to evaluate the efficacy of cabozantinib in combination with atezolizumab versus second NHT (abiraterone or enzalutamide) in subjects with mCRPC who have previously received one and only one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat mCSPC, M0 CRPC, and/or mCRPC, and who have measurable visceral disease or measurable extrapelvic adenopathy.

The multiple-primary efficacy endpoints comparing the experimental and control arms are:

- Duration of PFS per RECIST 1.1 with radiographic assessments by Blinded Independent Radiology Committee (BIRC)
- Duration of OS

The secondary efficacy endpoint is:

- ORR per RECIST 1.1 per BIRC

Additional endpoints are:

- PSA response rate
- Duration of radiographic response per RECIST 1.1 (per Investigator and BIRC)
- Duration of PFS as determined per Prostate Cancer Working Group 3 (PCWG3) criteria (Scher et al 2016) by BIRC
- Time to PSA progression
- Time to SSE

- Time to pain progression
- Time to chemotherapy
- Health care resource utilization
- Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health as assessed by the EuroQol Health questionnaire EQ-5D-5L and European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30
- Safety as assessed through the evaluation of adverse events (AEs), including immune-related adverse events (irAEs)
- Pharmacokinetics (PK) of cabozantinib given in combination with atezolizumab
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Correlation of immune cell, tumor cell, and plasma biomarker analyses with clinical outcomes

STUDY DESIGN

This is a Phase 3, multicenter, randomized, parallel group, open-label, controlled trial of the combination of cabozantinib (40 mg po qd) with atezolizumab (1200 mg IV q3W) versus second NHT (abiraterone or enzalutamide) in subjects with mCRPC (adenocarcinoma) who previously received one and only one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat mCSPC, M0 CRPC, and/or mCRPC and whose disease biochemically (PSA progression) or radiographically progressed on that NHT. PFS and OS are the multiple-primary endpoints. The primary analysis of PFS per RECIST 1.1 will be based upon radiographic assessments by BIRC. Approximately 580 eligible subjects who have mCRPC with measurable visceral metastasis or measurable extrapelvic lymphadenopathy, and whose disease is deemed to be worsening based on PSA or radiographic soft tissue progression in the opinion of the Investigator, will be randomized at approximately 280 sites in this trial.

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

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

Each subject's course of trial participation will consist of the following periods:

Pre-Treatment Period:

Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying screening assessments must be performed within 21 days before randomization unless otherwise specified. If there is a change in clinical status after screening and prior to randomization, these assessments are to be repeated as clinically indicated. Prior to randomization, the Investigator will designate in the interactive response technology (IRT) system the NHT (abiraterone, apalutamide, darolutamide, or enzalutamide) the patient previously received and progressed on. If eligible and randomized to the control group (second NHT), the IRT system will then dispense enzalutamide if the prior NHT was abiraterone; abiraterone if the

prior NHT was enzalutamide; and Investigator's choice of abiraterone or enzalutamide if the prior NHT was apalutamide or darolutamide.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive cabozantinib plus atezolizumab or second NHT, respectively. Based on treatment assignment, subjects will begin treatment on one of the following regimens:

Experimental Arm (290 subjects):

Cabozantinib (40 mg po qd) + atezolizumab (1200 mg IV q3w)

Control Arm (290 subjects):

Abiraterone (1000 mg po qd) + prednisone (5 mg po bid), OR enzalutamide (160 mg po qd)

Randomization will be stratified by the following factors:

- Liver metastasis (yes/no)
- Prior docetaxel for locally advanced or metastatic castration-sensitive prostate cancer (yes/no)
    - Response is "no" if subject previously had M0 CRPC
- First NHT given for mCRPC vs M0 CRPC vs metastatic castration-sensitive prostate cancer. Note: For subjects who have received the same NHT for both mCRPC and either mCSPC (including locally advanced M0 CSPC) or M0 CRPC, subjects should be stratified by the disease state for which they received their first NHT even if they did not progress on it then.

Subjects may receive study treatment, even after protocol-defined progression, until they are no longer clinically benefitting in the opinion of the Investigator, unless they 1) need subsequent systemic anticancer treatment or urgent tumor-directed alternative medical intervention (eg, to central nervous system [CNS] metastases), 2) experience unacceptable toxicity, or 3) have any other reason for treatment discontinuation as listed in the protocol. In the absence of such, continued treatment after radiographic progression may occur in subjects who meet both of the following criteria:

- Clinical benefit per Investigator judgment
- ECOG performance status 0 or 1

Crossover among treatment arms will not be allowed.

Post-Treatment Period:

A first Post-Treatment Follow-up Visit (FU-1) for safety assessment is to occur at least 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Radiographic tumor, PSA, health-related quality of life (HRQOL), and pain assessments are to continue, regardless of whether study treatment is given, reduced, held or

discontinued until a criterion for ending radiographic assessments is met (defined below in Tumor Assessments). Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

In addition, subjects are to be contacted every 8 weeks (± 7 days) after FU-2 to assess survival status and document receipt of nonprotocol anticancer therapy (NPACT). This will continue until the subject expires or the Sponsor decides to discontinue collection of these data in the study. Every effort must be made to collect these protocol-specified evaluations unless consent to provide these data is withdrawn.

Study Completion:

The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS in any of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results).

Maintenance Phase/Treatment after Study Completion:

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes to have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented.

In the Maintenance Phase, subjects on study treatment will continue to receive the study treatment(s) to which they were randomized until they meet a protocol-defined criterion for treatment discontinuation. Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests, ECGs, symptom-directed physical examination and vital signs) and tumor assessments every 12 weeks (or more frequently as clinically indicated) for as long as they are in this phase.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of serious adverse events (SAEs), certain AEs (including AEs of special interest [AESIs, Table 8-1; whether serious or not] and AEs leading to dose modifications or treatment discontinuation), and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

End of Trial:

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

NUMBER OF SUBJECTS

Approximately 580 subjects will be randomized in a 1:1 fashion to the cabozantinib and atezolizumab combination (290) and second NHT (290) treatment arms, respectively, at

approximately 280 global sites. The sample size may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined.

TARGET POPULATION

To be eligible for the study the subject must meet all inclusion criteria and no exclusion criteria. The Sponsor will not grant exceptions to these eligibility criteria.

Inclusion Criteria:

1. Men with histologically or cytologically confirmed adenocarcinoma of the prostate.

   Note: Neuroendocrine differentiation and other histological features are permitted if adenocarcinoma is the primary histology.
2. Subjects must have had a rising PSA or radiographically progressed on their prior treatment with one, and only one, NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) for castration-sensitive locally advanced (T3 or T4) or metastatic castration-sensitive prostate cancer, M0 CRPC, and/or mCRPC.

   Note: Subjects may have previously received taxane-based chemotherapy for locally advanced or metastatic castration-sensitive prostate cancer but no other approved or experimental nonhormonal systemic therapies for mCRPC.
3. Bilateral orchiectomy or ongoing ADT with a gonadotropin-releasing hormone (GnRH) agonist/antagonist (surgical or medical castration), with serum testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening.
4. Measurable (extrapelvic soft tissue) metastatic disease per Investigator assessment as defined by at least one of the following:
   a. Measurable visceral (eg, adrenal, kidney, liver, lung, pancreas, spleen) disease per RECIST 1.1, OR
   b. Measurable extrapelvic adenopathy (ie, adenopathy above the aortic bifurcation).
5. Progressive disease at study entry as defined by at least one of the following two criteria:
   a. Prostate specific antigen (PSA) progression defined by a minimum of 2 rising PSA values from 3 or 4 most recent consecutive assessments with an interval of at least 7 days between assessments.

      Note: If qualifying solely by PSA progression, the screening PSA value must be at least 2 ng/mL (2 μg/L), and the oldest qualifying value must have been based on a blood sample drawn no longer than one year prior to signing of the informed consent form (ICF); up to one PSA decrease is permitted as long as it is not the most recent value. If the study lab is the local lab at which the subject's previous PSA blood samples were drawn, then the screening local lab PSA must be the highest, OR
   b. Soft tissue disease progression (PD) in the opinion of the Investigator.

      Note: Subjects with bone disease progression alone are not eligible.
6. Age ≥ 18 years old or meeting country definition of adult, whichever is older, on the day of consent.
7. ECOG performance status score of 0 or 1.

8. Recovery to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy in the opinion of the Investigator.
9. Adequate organ and marrow function, based upon all of the following laboratory assessments from samples obtained within 21 days before randomization:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 × 10^9/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. Platelets ≥ 100,000/mm^3 (≥ 100 × 10^9/L) without transfusion within 2 weeks before screening laboratory sample collection.
    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 1 week before screening laboratory sample collection.
    d. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN)

       Note: Subjects with known Gilbert's disease or unconjugated hyperbilirubinemia who have serum bilirubin level ≤ 3 × ULN may be enrolled.
    e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both ≤ 3 × ULN. Subjects with known hepatic metastasis may enroll with serum ALT and AST both ≤ 5 × ULN.
    f. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation: (140 – age) × weight (kg)/(serum creatinine [mg/dL] × 72).
    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g.
    h. Negative hepatitis B surface antigen (HBsAg) test
    i. Negative hepatitis C virus (HCV) antibody test, or positive HCV antibody test followed by a negative HCV RNA test and no ongoing anti-HCV therapy.

       Note: The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
10. Understanding and ability to comply with the protocol requirements, including scheduled visits, treatment plan, laboratory tests, and all other study procedures. Evidence of a signed and dated ICF, indicating that the subject has been informed of all pertinent aspects of the study, prior to any screening assessments except those procedures performed as standard of care within the screening window.
11. Sexually active fertile subjects and their female partners must agree to use highly effective methods of contraception during the course of the study and for 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm). A barrier contraceptive method (eg, condom) is also required. In addition, men must agree not to donate sperm during these same periods.

Exclusion Criteria:

1. Only evidence of metastasis is adenopathy below the aortic bifurcation, non-measurable soft tissue (visceral or adenopathic) disease per RECIST 1.1, or bone-only disease.
2. Any prior systemic nonhormonal therapy initiated for the treatment of mCRPC.
3. Receipt of abiraterone within 1 week; cyproterone within 10 days; or receipt of flutamide, nilutamide, bicalutamide, enzalutamide, or other androgen-receptor inhibitors within 2 weeks before randomization.

   Note: Subjects receiving prior enzalutamide, bicalutamide, flutamide, or nilutamide monotherapy without ADT at the time of screening are not eligible, unless bilateral orchiectomy has already been performed.
4. Radiation therapy within 4 weeks (2 weeks for bone metastases) prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
5. Known brain metastases (symptomatic or non-symptomatic) or cranial epidural disease unless adequately treated with radiotherapy, radiosurgery, or major surgery (eg, removal or biopsy of brain metastasis) and clinically stable for at least 4 weeks prior to randomization.

   Note: Subjects who are neurologically symptomatic as a result of their CNS disease or receiving systemic corticosteroid treatment for their CNS disease are not eligible.
6. Symptomatic or impending spinal cord compression or cauda equina syndrome.
7. Concomitant anticoagulation with oral anticoagulants including, but not limited to, platelet inhibitors (eg, clopidogrel or ticagrelor), warfarin, dabigatran, and betrixaban, except for those specified below.
   a. Allowed anticoagulants are:
      i. Prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
      ii. Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before randomization and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
8. Administration of a live, attenuated vaccine within 30 days prior to randomization. The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.
9. Systemic treatment with, or any condition requiring, either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to randomization. Subjects with brain metastases requiring systemic corticosteroid at any dose are not eligible.

   Note: Prednisone (5 mg po bid) should be used with abiraterone. Inhaled, intranasal, intra-articular, and topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease (eg, in presence of adrenal metastasis). Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.

10. Uncontrolled, significant intercurrent or recent illness that may impede interpretation of safety data, including, but not limited to, the following conditions:
    a. Cardiovascular and cardiac disorders:
        i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, torsades de pointes) within 6 months before randomization.
        ii. Uncontrolled hypertension defined as systolic blood pressure (BP) > 150 mm Hg or diastolic BP > 90 mm Hg despite optimal antihypertensive treatment
        iii. Stroke, transient ischemic attack [TIA], myocardial infarction, or other symptomatic ischemic event or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism [DVT/PE]) within 6 months before randomization.

            Notes:

            Upon Sponsor approval, subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if asymptomatic and stable at screening and treated with LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban for at least 1 week before randomization.

            Non-symptomatic white matter disease in the brain is acceptable.
        iv. History of additional significant risk factors for torsades de pointes (eg, long QT syndrome)
    b. Neuropsychiatric disorder (including active suicidal ideation) likely to interfere with ability to give informed consent or comply with protocol requirements.
    c. Gastrointestinal (GI) disorders, including those affecting absorption or associated with a high risk of perforation or fistula formation:
        i. 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 (eg, Crohn's disease, ulcerative colitis)
        ii. Abdominal fistula, bowel obstruction, GI perforation, or intra-abdominal abscess within 6 months before randomization

            Note: Subjects with intra-abdominal abscesses are eligible if complete healing has been confirmed before randomization.
    d. Hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, clinically significant hematuria, hematemesis, coagulopathy, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.
    e. Known cavitating pulmonary lesion(s) or known endobronchial disease manifestation.
    f. Lesions invading major pulmonary blood vessels.
    g. Other clinically significant disorders, such as:

i. Any active, known or suspected autoimmune disease (see Appendix F for a comprehensive list of autoimmune diseases and immune deficiencies).

Note: Subjects with type I diabetes mellitus, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

ii. Any active infection requiring systemic treatment.

Note: Subjects receiving oral (including prophylactic) antibiotics with no symptoms of infection at randomization or oral valacyclovir (valaciclovir) are eligible.

iii. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

Note: HIV testing will be performed at screening if and as required by local regulation.

iv. Active tuberculosis.

v. Known history of COVID-19 unless the subject has demonstrated recovery from the disease at least 30 days prior to randomization.

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

vii. Serious non-healing wound/ulcer/bone fracture per Investigator judgment.

viii. Clinically significant malabsorption syndrome per Investigator judgment.

ix. Pharmacologically uncompensated, symptomatic hypothyroidism.

Note: Asymptomatic hypothyroidism only requiring hormone replacement is allowed.

x. Moderate to severe hepatic impairment (Child-Pugh B or C) or known cirrhosis.

xi. Requirement for hemodialysis or peritoneal dialysis.

xii. History of solid organ transplantation

xiii. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
-Patients with indwelling cathethers (e.g. PleurX®) are allowed

11. Major surgery (eg, prostatectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks prior to randomization. Minor surgeries (eg, fine-needle biopsy) within 10 days prior to randomization. Subjects must have complete wound healing from major surgery or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
12. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 21 days before randomization.

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

    Note: This requirement does not apply if the subject has a permanent cardiac pacemaker in place or a history of asymptomatic bundle branch block in the absence of cardiac ischemia.

13. Inability or unwillingness to swallow tablets or receive IV administration.
14. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe infusion-related reactions to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.
15. Any other active malignancy at time of randomization or diagnosis of another malignancy within 2 years prior to randomization that requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, or carcinoma in situ of the breast.

ESTIMATED LENGTH OF SUBJECT PARTICIPATION

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

ESTIMATED STUDY DATES

It is estimated that approximately 24 months will be required to randomize 580 subjects. The numbers of events required for the primary analyses of PFS (202 events among the first 324 randomized subjects) and OS (340 events among all 580 randomized subjects) are expected to be observed approximately 21 months and 37 months (final OS analysis), respectively, after the first subject is randomized. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. These estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation.

STUDY TREATMENT REGIMEN DOSE/ ROUTE/ DURATION

Subjects in the experimental arm will take oral study medication (40 mg of cabozantinib: 2 tablets containing 20 mg each of cabozantinib) qd, and atezolizumab will be administered at a standard dosing regimen of 1200 mg as an IV infusion q3w. Two dose reduction levels of cabozantinib will be allowed in the experimental arm (20 mg qd and 20 mg every other day [qod]). Dose reductions for atezolizumab will not be allowed, but AEs may be managed by dose delays.

Subjects in the control arm will receive abiraterone 1000 mg po qd with prednisone 5 mg po bid, or enzalutamide 160 mg po qd as designated by the Investigator prior to randomization and as per local prescribing information. Dose interruptions and reductions will be allowed as per local prescribing information.

Subjects will continue study treatment until they no longer clinically benefit in the opinion of the Investigator or until unacceptable toxicity, the need for alternative systemic anticancer treatment, or another reason for treatment discontinuation (Section 5.6.6.2).

EFFICACY ASSESSMENTS

Subjects will be monitored for radiographic response and progression per RECIST 1.1. Determination of the multiple-primary endpoint, PFS, and of the secondary endpoint, ORR, will

be per radiographic assessments performed by BIRC. The additional endpoint of PFS per PCWG3 will be determined by soft tissue progression based on CT/MRI per RECIST 1.1 or bone disease progression based on bone scan per PCWG3 and will be assessed by BIRC.

Subjects will be assessed for survival through the FU-2 visit and every 8 weeks (± 7 days) after that.

TUMOR ASSESSMENTS

Chest / Abdomen / Pelvis (CAP): CT of CAP or chest CT and abdomen/pelvis MRI will be performed in all subjects at screening prior to randomization. Tumor assessments after randomization are to be performed every 9 weeks ± 7 days through Week 28 (ie, the first three on-study tumor assessments), and then every 12 weeks ± 7 days as per PCWG3 guidelines. Additional imaging of potential disease sites should be performed whenever radiographic disease progression is suspected.

Brain: MRI (or CT) of the brain will be performed only if clinically indicated at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis or if clinically indicated following the same post-baseline frequency as the imaging for CAP. MRI is the preferred method for brain scans. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless contraindicated. Note: For eligibility requirements regarding prior treatment of brain metastasis, refer to Section 4.3.

Bone: Technetium-99m bone scans (TBS) are to be performed at screening for all subjects. Evidence of or suspicion for soft tissue masses extending from bone must be corroborated with CT at screening. If a screening CT scan shows measurable soft tissue disease extending from bone, that soft tissue disease must be followed by on-study CT when CAP imaging (not capturing the lesion) is done. After randomization, TBS are to be performed on all subjects on the same schedule as for CAP. Subjects who report new symptoms associated with new or worsening bone scan lesions must have bone-directed CT performed (unless already captured by routine CT), which are to continue on the same schedule as for CAP.

Subjects who are treated beyond radiographic disease progression will continue to undergo tumor assessments at the frequency described above until study treatment is discontinued.

The same imaging modalities used at screening must be used for subsequent tumor assessments after randomization. If there is clinical concern regarding the administration of contrast at screening, then a non-contrast CAP imaging study is acceptable as a screening assessment if it clearly demonstrates measurable soft tissue disease that can be followed without the need for contrast. If, at a follow-up imaging time point, the use of contrast is prohibited (eg, due to acquired renal impairment or contrast allergy), then the same modality should be used without contrast.

Tumor assessments should continue on the protocol-defined schedule relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued.

Radiographic response and PD will be determined centrally using RECIST 1.1 (by Investigator and BIRC) and PCWG3 guidelines (by BIRC only). Investigators are encouraged to continue study treatment and imaging until the subject is no longer clinically benefitting.

Radiographic tumor assessments are to continue under the following guidelines:

Subject Status		Action with Radiographic Assessments
Study Treatment Discontinued?	**Investigator-Assessed rPD per RECIST 1.1 Reached?**	
No	No	Continue radiographic assessments
No	Yes	Continue radiographic assessments (ie, Investigator-assessed clinical benefit after radiographic progression)
Yes	No	Continue radiographic assessments unless receipt of new systemic therapy has been documented
Yes	Yes	Radiographic assessments discontinued

rPD, radiographic progressive disease; RECIST 1.1, Response Evaluation Criteria for Solid Tumors version 1.1.

For the purpose of determining radiographic study endpoints, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments will be promptly sent to the BIRC until the primary analysis for the primary endpoint of PFS is completed. The BIRC will also review prior radiation history data for the purpose of selection of target lesions.

PROSTATE-SPECIFIC ANTIGEN ASSESSMENTS

Serum PSA levels will be assessed in all subjects at screening. Subsequent assessments will occur with scheduled imaging. PSA assessments should not be used to make study treatment decisions in this study.

OVERALL SURVIVAL FOLLOW-UP ASSESSMENTS

Overall survival will be assessed every 8 weeks (± 7 days) after the FU-2 visit. Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data.

SAFETY ASSESSMENTS

Safety will be assessed on a schedule based on the date of first dose. Routine safety assessments will be done at least every 3 weeks (± 3 days). All serious adverse events (SAEs) occurring any time after informed consent must be reported to the Sponsor or designee within 24 hours. The safety follow-up visit (FU-1) will be performed 30 (+14) days after the date of the decision to permanently discontinue study treatment.

Monitoring will continue for SAEs and AESIs (whether serious or not) through 100 (± 14) days after the date of the decision to permanently discontinue study treatment (FU-2 visit). Related AEs leading to study treatment discontinuation, AESIs, and related SAEs will continue to be followed until resolution (event is fully resolved, ≤ Grade 2 severity, or is deemed stable or irreversible by the Investigator).

Safety assessments include AE review, directed physical examination, vital signs, performance status, 12-lead ECG, hematology, serum chemistry, coagulation tests, urine tests (including UPCR and components), and thyroid function tests. AE seriousness, severity grade, relationship to study treatment, and relationship to immune effects (ie, irAEs) will be assessed by the Investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v5.

An Independent Data Monitoring Committee (IDMC) will be established to monitor safety of the study on a regular basis. The IDMC will operate independently from the Sponsor and the clinical investigators. In addition, the Sponsor has an established internal safety governance structure, which oversees the monitoring of the safety and benefit-risk profile for all investigational products on an ongoing basis across all ongoing company-sponsored clinical studies.

HEALTH-RELATED QUALITY OF LIFE (HRQoL)

Health-related quality of life assessments will be performed using the EuroQol Health questionnaire EQ-5D-5L and EORTC questionnaire QLQ-C30. Subjects will be requested to complete the assessment at baseline (prior to first dose of study treatment on RSV1) and with scheduled imaging (prior to image acquisition) thereafter. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects. Subjects themselves should complete the questionnaire on the day of the visit prior to seeing study site personnel. HRQOL assessments will no longer be collected for subjects who transition to the Maintenance Phase.

PAIN ASSESSMENTS

Assessment of pain will be self-reported by each subject using an 11-point (from 0 to 10) numeric rating scale (NRS) measuring worst pain in the last week, with 0 representing “No Pain” and 10 representing “Pain as Bad as You Can Imagine”.

Assessments of baseline pain will be performed prior to first dose of study treatment on RSV1, and subsequent pain assessments will be performed with scheduled imaging (prior to image acquisition). In addition, for analgesics taken for at least seven consecutive days, the Investigator will continuously assess new or increased use relative to baseline.

These assessments are to continue regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects. Pain assessments will no longer be collected for subjects who transition to the Maintenance Phase.

SYMPTOMATIC SKELETAL EVENTS

Symptomatic skeletal events (SSEs) will be continuously assessed from RSV1 through the FU-2 visit. The definition of an SSE is an instance of any one of the following: radiation therapy to bone, surgery to bone, spinal cord compression, or symptomatic fracture.

HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization parameters will be collected from randomization through the FU-2 visit. These include hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions. These data will not be collected in the Maintenance Phase.

BIOMARKERS

The schedule of biomarker assessments is specified in Appendix A and Appendix B. The samples include:

- Tumor samples (archival or fresh tumor biopsy; recommended but not required)
  - If archival tumor tissue is not available, a fresh tumor biopsy may be obtained prior to first dose of study treatment.
  - A fresh tumor tissue biopsy may also be performed at disease progression.
- Peripheral blood

Exploratory analyses may include but are not limited to the following:

- Targets of the study drugs (eg, PD-L1, MET) and relevant biomarker expression levels
- Tumor characteristics (eg, immune cell infiltration, tumor mutational burden [TMB]) in tumor specimens
- Plasma biomarkers (eg, cytokines/chemokines)
- Circulating tumor cells (CTCs)
- Circulating tumor DNA (ctDNA)

A pharmacogenetic blood sample will be collected predose on the first day of treatment (RSV1) and may be used for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with the pharmacokinetics, safety, tolerability, and/or response to the study drug combination. This sample may also be used for assay development to facilitate identification of novel predictive biomarker profiles and improve treatment strategies.

Collection of biomarker samples may be halted early or sampling frequency may be modified at the discretion of the Sponsor. These samples will no longer be collected if the study transitions to the Maintenance Phase.

PHARMACOKINETICS

Blood samples will be obtained from all subjects in the cabozantinib plus atezolizumab combination arm. Samples will be collected for plasma cabozantinib concentration measurement predose on RSV1, RSV2, RSV3, RSV4, and RSV5. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib taken in combination with atezolizumab in this population.

Serum concentrations of atezolizumab will be measured in the cabozantinib plus atezolizumab combination arm. Samples will be collected for serum atezolizumab concentration measurement predose on RSV1, RSV3, RSV5, RSV9, RSV16, RSV19, and FU-1 and FU-2 visits. The results will be used to confirm exposure to atezolizumab.

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

IMMUNOGENICITY ASSESSMENTS

Blood samples will be obtained from all subjects in the cabozantinib plus atezolizumab combination arm for immunogenicity assessment (anti-drug antibodies [ADA]) predose on RSV1, RSV3, RSV5, RSV9, RSV16, RSV19, and FU-1 and FU-2 visits. Samples may be analyzed for neutralizing ADA response to atezolizumab if ADA testing is positive, as applicable.

STATISTICAL METHODS

The multiple primary efficacy analyses in this study are comparisons of duration of PFS per RECIST 1.1 per BIRC and duration of OS in subjects treated with cabozantinib in combination with atezolizumab (the experimental arm) versus second NHT (the control arm). Treatment with cabozantinib in combination with atezolizumab will be inferred to be superior to treatment with second NHT if the null hypothesis of no difference between arms is rejected for either OS or PFS in favor of the combination arm. Inflation of Type 1 error associated with multiple primary endpoints and a single secondary efficacy endpoint will be controlled by a closed testing procedure that employs modified Bonferroni, gatekeeping, and fallback methods. The study-wise 2-sided alpha of 0.05 will be nominally divided between multiple primary endpoints PFS (0.002) and OS (0.048) with alpha allocations passed from significant endpoints to those to be tested next per the pre-specified testing strategy.

For the primary analyses, PFS is defined as time from randomization to PD per RECIST 1.1 as determined by the BIRC or death from any cause and OS is defined as time from randomization to death due to any cause.

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

The study is designed to provide adequate power for both PFS and OS endpoints. Compared with OS, a smaller sample size is needed to provide reasonable power for PFS. As a result, the number of events necessary to trigger the primary analysis of PFS could be reached before the study is fully accrued, and PFS events could be biased toward shorter progression times were PFS evaluated in the larger sample size required for OS. Thus, to reduce bias toward shorter progression times, this study employs a “trial within a trial” design (Hessel et al 2016) to allow longer, more robust PFS follow-up among fewer subjects than the total required for OS. Futility and interim analyses of PFS are not planned.

For PFS, a total of 202 events in the first 324 subjects randomized in the combination and second NHT control arms provide the study with 90% power for a 2-sided log-rank test with a 0.002 level of significance to detect a hypothesized true HR of 0.54. Assuming an exponential distribution of PFS, this corresponds to an 85% increase in median PFS from 4 months to 7.4 months. In the current design, the minimum observed effect that would result in statistical significance for PFS is a HR of 0.65, a 55% improvement in median PFS from 4 to 6.2 months. For OS, a total of 340 deaths among all 580 subjects randomized in the combination and second

NHT arms are required to provide 90% power to detect an HR of 0.70 using the log-rank test and a 2-sided significance level of 0.048. Assuming an exponential distribution for OS, this corresponds to a 43% increase in median survival from 14 months to 20 months. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS is an HR of 0.80, a 25% improvement in median from 14 to 17.5 months.

Two interim analyses of OS are planned and will include all subjects randomized to combination and second NHT control arms at the time of each analysis. The first interim analysis of OS will be conducted at the time of primary analysis of PFS. This is expected to occur at approximately the 32% information fraction for OS. The second interim analysis of OS is planned at approximately the 76% information fraction. Inflation of Type 1 error associated with these interim analyses will be controlled using Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending functions based upon a total alpha allocation for OS that depends upon whether the PFS result is significant. If the null hypothesis of no difference in OS is rejected at a planned interim OS analysis in favor of the experimental arm, no subsequent testing of OS is planned.

With an average accrual rate of ~24 subjects per month and using a 1:1 treatment allocation ratio between the combination and control arms, a total of 580 subjects (290 subjects in each arm) are required to observe the required number of events within the planned study duration (approximately 24 months accrual; approximately 21 months to observe the required PFS events and approximately 37 months to observe the required deaths for OS). The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. The estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation. The sample size may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined.

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ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibodies, also called anti-therapeutic antibodies
ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration time curve
Bid	Twice daily
BIRC	Blinded Independent Radiology Committee
BP	Blood pressure
BRCA1(2)	Breast cancer 1(2)
BUN	Blood urea nitrogen
CAP	Chest / Abdomen / Pelvis
CAR	Chimeric antigen receptor
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
CrCl	Creatinine clearance
(e)CRF	(electronic) Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine-release syndrome
CSC	Clinical Steering Committee
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CYP	Cytochrome P450
DICOM	Digital Imaging and Communications in Medicine

DILI	Drug-induced liver injury
dMMR	deficient mismatch repair
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
DVT	Deep vein thrombosis
EC	Ethics committees
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ERBT	External beam radiotherapy
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTP	File Transfer Protocol
FU-1(2)	Follow-up visit 1(2)
FXa	Factor Xa
GCP	Good clinical practice
G(M)-CSF	Granulocyte colony-stimulating factors
GGT	γ-glutamyltranspeptidase
GLP	Good Laboratory Practice
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
H_0	Null hypothesis
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HPMC	Hydroxypropyl methylcellulose
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQOL	Health-related quality of life
HTTP	HyperText Transfer Protocol
IC_{50}	Concentration required for 50% target inhibition
IC(F)	Informed consent (form)
ICH	International Council on Harmonization
ICI	Immune checkpoint inhibitor

IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
irAE	Immune-related adverse event
IRB	Institutional Review Boards
irPR	Immune-related partial response
IRR	Infusion-related reaction
irRC	Immune-related response criteria
irRECIST	Immune-related RECIST
ITT	Intent to treat
IV	Intravenous
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
LD-OF	Lan-DeMets O'Brien-Fleming
LFT	Liver function test
LH	Luteinizing hormone
LMWH	Low molecular weight heparin
M0	Non-metastatic
(m)CRPC	(metastatic) Castration-resistant prostate cancer
(m)CSPC	(metastatic) Castration-sensitive prostate cancer
MAS	Macrophage activation syndrome
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
MTC	Medullary thyroid cancer
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHT	Novel hormonal therapy
NIH	National Institutes of Health
NK	Natural killer
NPACT	Nonprotocol anticancer therapy
NR	Not reached
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ONJ	Osteonecrosis of the jaw
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease

PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
PITT	PFS Intent-to-Treat
PK	Pharmacokinetic
po	Per os (orally administered)
PPE	Palmar-plantar erythrodysesthesia
PPI	Proton pump inhibitor
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate specific antigen
PSADT	PSA doubling time
PT/INR	Prothrombin time/international normalized ratio
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
QD	Once daily
QOD	Every other day
QTcF	Corrected QT interval by Fridericia
RBC	Red blood cell
RCC	Renal cell carcinoma
RF	Radiofrequency
RLPS	Reversible posterior leukoencephalopathy syndrome
RNA	Ribonucleic acid
RSV	Routine safety visit
PFS	Radiographic progression-free survival
rPD	Radiographic progressive disease
RSI	Reference safety information
RTK	Receptor tyrosine kinase
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of product characteristics
SOC	Standard of care
SoD	Sum of the diameters
SSE	Symptomatic skeletal events
T3	Triiodothyronine
T4	Thyroxine
$t_{1/2}$	Terminal half-life
TBS	Technetium-99m bone scans

TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
t_{max}	Observed time to reach peak plasma concentration
TMB	Tumor mutational burden
TNBC	Triple negative breast cancer
TPR	Target lesion time point response
TSH	Thyroid-stimulating hormone
UA	Urinary analysis
UC	Urothelial cancer
UE	Unable to evaluate
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
uPR	Unconfirmed partial response
US PI	United States prescribing information
VAD	Ventricular assist device
VAS	Visual analog rating scale
VEGF(R)	Vascular endothelial growth factor (receptor)
WBC	White blood cell

1 BACKGROUND

1.1 Prostate Cancer

In 2018, prostate cancer was the fourth most commonly diagnosed malignancy worldwide behind cancers of the lung, breast, and colorectum (GLOBOCAN 2018). Incident prostate cancer was reported in 1.3 million men and accounted for 7.1% of all new cancer diagnoses that year. It is the most common cancer among men worldwide and the second leading cause of cancer deaths in the US (Bashir 2015), where its incidence in 2018 exceeded that of cancers of the bladder, kidney and testis combined (NIH NCI SEER 2018).

There are multiple histologic types of prostate cancer but adenocarcinoma accounts for the vast majority of cases. Prostate adenocarcinoma typically is associated with elevation in the serum prostate-specific antigen (PSA) and often responds to testosterone-lowering (castration) and other hormonal manipulations targeting signaling through the androgen receptor (AR) axis.

Prostate adenocarcinoma is radiographically localized at diagnosis in the majority of cases where PSA testing is widely implemented. Approximately two-thirds of men with radiographically localized disease are cured with definitive localized therapy (radical prostatectomy or radiotherapy) but the remainder will experience recurrence heralded by a rising PSA, local radiographic occurrence and/or metastases. Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced or metastatic prostate cancer due to the androgen dependency of this disease. A rising PSA without radiographically evident metastases despite initiation of ADT castration signifies a non-metastatic castration-resistant state (non-metastatic castration-resistant prostate cancer [M0 CRPC]). *De novo* metastatic disease (metastatic castration-sensitive prostate cancer [mCSPC]) accounts for 3-7% of new cases of prostate cancer in developed nations and its incidence in the US may be rising due to recent declines in population-based PSA surveillance (Weiner et al 2016). Furthermore, *de novo* metastatic disease is commonly diagnosed in countries where PSA testing is not part of standard clinical practice. M0 CRPC and mCSPC (including locally advanced M0 CSPC) are the primary pathways to metastatic castration-resistant prostate cancer (mCRPC), which all subjects enrolling in this Phase 3 study are required to have.

Treatment of mCRPC

Systemic treatment alternatives for patients with metastatic castration-resistant prostate cancer (mCRPC) now include chemotherapy, immunotherapy, androgen signaling pathway receptor inhibitors, radionuclide therapy, and PARP inhibitors (Tannock et al 2004, de Bono et al 2010, de Bono et al 2011, Kantoff et al 2010, Parker et al 2013, Ryan et al 2015, Scher et al 2012, Beer et al 2014, Beer et al 2017, de Bono et al 2020, Abida et al 2020; Sartor et al 2021).

Treatment of locally advanced or metastatic CSPC

ADT has historically been used to treat *de novo* metastatic disease or metastatic castration-sensitive disease preceded by radiographically localized disease. However, docetaxel/prednisone and novel hormonal therapies (NHTs), including abiraterone, apalutamide and enzalutamide have been shown to improve outcomes when combined with ADT initiation (Sweeney et al 2015, Kyriakopolous et al 2018, James et al 2016, Fizazi et al 2017, Fizazi et al [Lancet Oncol] 2019, Armstrong et al 2019, Chi et al 2019).

Treatment of M0 CRPC

ADT (potentially with salvage radiotherapy) may be initiated for a rising PSA detected after failure of definitive localized therapy with curative intent for radiographically localized disease. Patients who develop PSA progression while receiving ADT without evident metastasis are defined as having M0 CRPC, an alternative path to mCRPC distinct from mCSPC (including locally advanced M0 CSPC). For these M0 CRPC patients, three AR antagonists (apalutamide, enzalutamide, and darolutamide) have demonstrated improvements in metastasis-free survival (MFS) and overall survival (OS) compared with placebo in men with a PSA doubling time less than 10 months (Smith et al 2018, Hussain et al 2018, Fizazi et al [NEJM] 2019, Sternberg et al 2020, Fizazi et al 2020, Smith et al 2021).

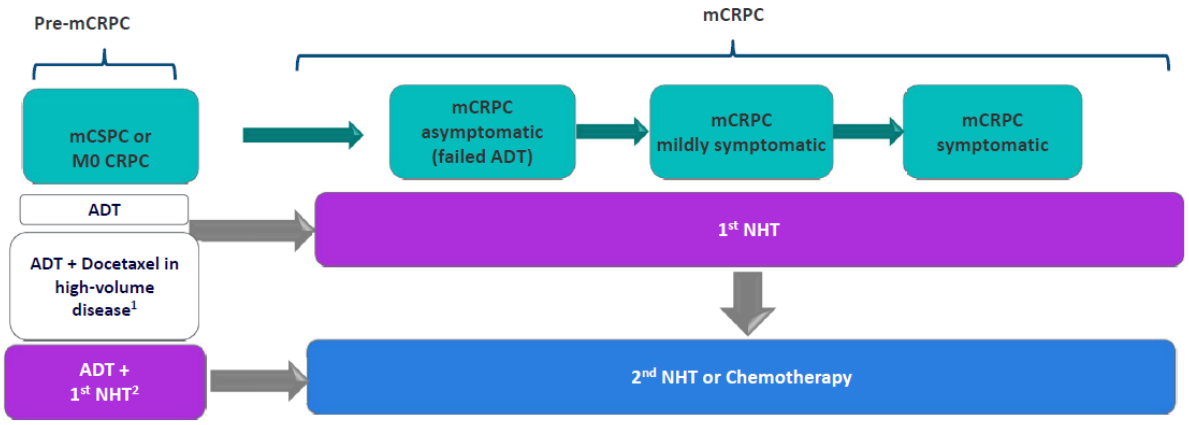
Clinically useful molecular and genomic characterization enabling confident prediction of the aggressiveness of incident prostate cancer is still largely lacking, although variables such as the Gleason score, time to castration resistance, PSA doubling time (PSADT), presence or absence of visceral disease, extent of osseous metastases, and genomic status regarding DNA damage response gene (eg, BRCA1, BRCA2) mutations and microsatellite instability or mismatch repair deficient status may assist the clinician in counseling the patient with advanced disease as to the need for aggressive or targeted therapy.

Potentially linked to the recent introduction of new treatments earlier in disease, the incidence of visceral metastases in men with mCRPC may be increasing and is associated with a particularly poor prognosis, particularly in the setting of liver disease (Nafissi et al 2019, Iwamoto et al 2018, Pezaro et al 2014, Whitney et al 2017). While patients with visceral disease were permitted to participate in the PREVAIL trial of enzalutamide in pre-chemotherapy mCRPC (Beer et al 2014) and the LATITUDE trial of abiraterone plus prednisone with ADT in high risk mCSPC (Fizazi et al 2017), these patients have a particularly dire unmet need upon progression on their first NHT (enzalutamide and abiraterone, respectively), which this Phase 3 study proposes to meet prior to

adequately fit patients having to resort to taxane-based chemotherapy with its attendant toxicities, and irrespective of when the first NHT was taken.

Standard-of-care therapies used for patients with visceral disease include taxane-based chemotherapy and NHTs (NCCN [Prostate Cancer v2.2019] 2019). Apart from their approvals in pre- and post-chemotherapy mCRPC, NHTs abiraterone, apalutamide, and enzalutamide have prolonged OS and PFS in combination with ADT in mCSPC while apalutamide, enzalutamide, and darolutamide have prolonged MFS and OS in M0 CRPC. However, none of these treatments is likely curative, and, upon progression, many patients with mCRPC will likely have already been treated with an NHT either as their first treatment for mCRPC or earlier disease (mCSPC [including locally advanced M0 CSPC] or M0 CRPC), respectively (Figure 1).

Figure 1: Prostate Cancer Treatment Algorithm



[1]No docetaxel given for M0 CRPC
[2]Abiraterone, enzalutamide, apalutamide, daralutamide
ADT, androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer

Despite recent progress in the systemic therapy of mCSPC (including locally advanced M0 CSPC), M0 CRPC and mCRPC, patients with visceral metastases or extrapelvic adenopathy have limited treatment options if they have already been treated with an NHT given the restriction of radium-223 use to patients with no known visceral disease; sipuleucel-T's relatively better efficacy in patients with indolent, low volume disease; pembrolizumab's restriction to men with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors; PARP inhibitors' current restriction to men with homologous recombination deficiency (HRD)-positive (eg, BRCA) disease; and 177-lutetium-617-PSMA's current restriction to men with PSMA-positive disease who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. As such, the proposed study design

defines a patient population with high unmet need and is further supported by the encouraging data from the ongoing Phase 1b XL184-021 study (Section 1.4).

1.2 Cabozantinib

Cabozantinib (XL184) is a potent, orally bioavailable inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization, including the vascular endothelial growth factor receptor (VEGFR2), MET, RET, and KIT. Somatic KIT mutations have been associated with aggressive forms of prostate cancer (Martinez-Gonzalez et al 2018). Cabozantinib targets also include TYRO3, AXL, and MER (TAM family kinases) and are implicated in promoting suppression of an antitumor immune response.

AXL and MER participate in the innate immune response where they function as regulators of inflammation by inhibiting activities mediated by dendritic cells and support maturation of NK cells. Their activation is part of a negative feedback loop that reduces the inflammatory process and tissue damage through engagement of inflammatory cytokine receptors (Rothlin et al 2015). Activation of the TAM receptors in macrophages mediates the transition from the M1 to M2 phenotype and the latter results in reduction of CD8+ T cells in tumors (Cook et al 2013, Myers et al 2019).

The receptor tyrosine kinase MET plays important roles in cell motility, proliferation, and survival, and has been shown to be a key factor in tumor angiogenesis, invasiveness, and metastasis. The effect of MET on immune cell activity was observed in preclinical solid tumors models, where blocking MET impeded neutrophil recruitment to tumors and lymph nodes and this activity potentiates T cell anti-tumor immunity (Glodde et al 2017). Prominent expression of MET has been observed in primary and metastatic prostate carcinomas (Pisters et al 1995, Humphrey et al 1995) with evidence for higher levels of expression in bone metastases compared to lymph node metastases or primary tumors (Knudsen et al 2002, Zhang et al 2010). Overexpression of HGF, the ligand for MET, has also been observed in prostate carcinoma (Zhu et al 2000), and increased plasma levels of HGF in CRPC are associated with decreased overall survival (Humphrey et al 2006).

Data from preclinical studies suggest that both HGF and MET are regulated by the androgen signaling pathway in prostatic tissue. Both proteins are expressed at low levels in xenograft models of androgen-sensitive prostate cancer but are upregulated in CRPC models (Humphrey et al 1995, Verras et al 2007). MET expression increases substantially in androgen-sensitive tumor cells after androgen withdrawal (Humphrey et al 1995, Verras et al 2007). Administration of a MET kinase inhibitor after castration reduced tumor cell proliferation in a preclinical model

of CRPC (Tu et al 2010). These observations indicate that upregulation of MET signaling may be associated with and contribute to the emergence of resistance to androgen suppression in prostate cancer.

VEGF and its receptors are key mediators in the process of tumor neoangiogenesis, invasion, and dissemination (Carmeliet and Jain 2011). In prostate cancer, elevated VEGF in either plasma or urine is associated with shorter overall survival (Bok et al 2001, George et al 2001). VEGF may also play a role in activating the MET pathway in tumor cells by binding to neuropilin-1, which is frequently upregulated in prostate cancer and appears to activate MET in a co-receptor complex (Zhang et al 2010).

Cabozantinib tablets (60 mg) are approved in the United States, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx® US Prescribing Information [PI] and European Medicines Agency [EMA] Summary of Product Characteristics [SmPC]). Cabozantinib tablets have also been approved in the US and other regions for the treatment of hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib and in the US for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible (HCC: 60 mg; DTC: 40 mg [in pediatric patients $\geq$ 12 years with body surface area (BSA) < 1.2 m^2] and 60 mg [in adult and pediatric patients $\geq$ 12 years with BSA $\geq$ 1.2 m^2]; Cabometyx US PI). The EU has also approved cabozantinib for similar use in adults but not in pediatric patients (Cabometyx EMA SmPC). Cabozantinib tablets (40 mg) are also approved for advanced RCC as a first-line treatment in combination with nivolumab. Cabozantinib capsules (140 mg) are approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq® US PI and EMA SmPC). The capsule and tablet formulations are not bioequivalent or interchangeable.

Following encouraging preliminary results for cabozantinib-treated CRPC subjects in a Phase 2 study (Smith et al 2013, Smith et al 2014, Basch et al 2015; NCT00940225), a randomized, double-blind, active-controlled Phase 3 study (COMET-1) was conducted to evaluate cabozantinib (60 mg po qd) vs prednisone (5 mg po bid) in 1028 men with bone-metastatic mCRPC who had previously been treated with docetaxel and at least one NHT (abiraterone acetate/prednisone and/or enzalutamide [Smith et al 2016; NCT01605227]). Subjects may have also received cabazitaxel at study entry, and there was no limit to the number of prior treatments allowed. In this study, cabozantinib significantly improved neither the primary endpoint OS

(11.0 vs 9.8 months; hazard ratio [HR] = 0.90 [95% confidence interval {CI}: 0.76, 1.06; stratified log-rank p = 0.21]) nor PSA outcomes compared with prednisone. Improvement in median radiographic progression-free survival (PFS) per Investigator was observed in the cabozantinib group (5.6 vs 2.8 months; HR = 0.48 [95% CI: 0.40, 0.57; p < 0.001]), as were improvements in circulating tumor cell (CTC) conversion, bone biomarkers, and symptomatic skeletal event (SSE) incidence. The improvement noted in CTC conversion from ≥ 5 CTCs/7.5 mL blood at baseline to < 5 CTCs/7.5 mL blood (cabozantinib 33% vs prednisone 6%) is notable given the association between CTC counts and OS (Heller et al 2018).

The discordance in results comparing OS with PFS observed in COMET-1 may be related to the inclusion of late (third, fourth, or fifth) lines of disease when dramatic improvements in outcomes may be difficult to obtain and demonstrate, and to differences in post-progression therapies (eg, cabazitaxel). Grade 3 to 4 adverse events (AEs) and treatment discontinuations due to AEs were higher with cabozantinib than with prednisone (71% vs 56% and 33% vs 12%, respectively), which may also partly be explained by the inclusion of subjects with late line disease. It is worth noting that this trial enrolled subjects in third- or later-line mCRPC where no therapy had yet proved efficacious; nevertheless, there was a trend (albeit statistically non-significant) in OS favoring cabozantinib in addition to positive findings on PFS favoring cabozantinib. Furthermore, an OS benefit among subjects who received cabozantinib was observed in a posthoc subgroup analysis of those with visceral disease enrolled in COMET-1. Of 191 subjects (133 cabozantinib, 58 placebo) with visceral metastases, the median OS was 7.1 months for those randomized to cabozantinib as compared with 4.8 months for those on prednisone (stratified HR = 0.63 [95% CI: 0.44, 0.92; p = 0.018]). In addition, a PFS benefit was also observed in this analysis of those with visceral disease; the median PFS per Investigator (including bone scan data) was 3.0 months for those randomized to cabozantinib as compared to 2.6 months for those on prednisone (HR 0.38 [95% CI: 0.25, 0.58]). The PFS benefit associated with cabozantinib treatment was noted regardless of whether bone scan data (showing two or more new lesions not consistent with tumor flare) informed the PFS endpoint (see Table 1-1), which suggests that PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 is a suitable multiple primary endpoint.

Table 1-1: COMET-1 Posthoc Subgroup Analysis

Population	**ITT**		**Visceral Mets at Baseline Subgroup**		**No Visceral Mets at Baseline Subgroup**	
All durations in months	Cabo (N=682)	Pred (N=346)	Cabo (n=133)	Pred (n=58)	Cabo (n=549)	Pred (n=288)
OS Median (95% CI)	11.0 (10.1, 11.6)	9.8 (9.0, 11.5)	7.1 (5.7, 8.6)	4.8 (3.5, 7.5)	11.8 (11.1, 12.9)	11.5 (9.8, 12.7)
HR (95% CI)	*0.90 (0.76, 1.06)*		*0.63 (0.44, 0.92)*		*0.92 (0.76, 1.12)*	
PFS per INV (incl TBS PD) Median (95% CI)	5.6 (5.5, 5.6)	2.8 (2.8, 2.9)	3.0 (2.8, 5.2)	2.6 (2.0, 2.6)	5.7 (5.6, 7.1)	2.8 (2.8, 3.0)
HR (95% CI)	*0.48 (0.40, 0.57)*		*0.38 (0.25, 0.58)*		*0.46 (0.38, 0.56)*	
PFS per INV (w/o TBS PD) Median (95% CI)	7.4 (5.8, 8.3)	5.1 (3.1, 5.5)	3.1 (2.8, 5.3)	2.6 (2.3, 2.7)	8.3 (8.1, 9.9)	5.5 (4.6, 5.8)
HR (95% CI)	*0.59 (0.48, 0.73)*		*0.44 (0.28, 0.68)*		*0.56 (0.44, 0.72)*	

cabo, cabozantinib; CI, confidence interval; HR, hazard ratio; INV, investigator; ITT, intent-to-treat; mets, metastases; OS, overall survival; PD, progressive disease; PFS, progression free survival; pred, prednisone; TBS, technetium bone scan; w/o, without

1.3 Atezolizumab and Other Immune Checkpoint Inhibitors

Atezolizumab

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

Atezolizumab injection for intravenous (IV) use (1200 mg once every 3 weeks [q3w]) has been approved in the US and the EU for the treatment of adult patients with advanced urothelial carcinoma (UC) after prior platinum-containing chemotherapy or in a subset of patients who are considered cisplatin-ineligible (different patient populations are indicated depending on region;

Rosenberg et al 2016, Balar et al 2017). Atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin has been approved in US for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. Atezolizumab is also approved for adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (Fehrenbacher et al 2016; Tecentriq™ US PI and EMA SmPC). Atezolizumab was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). In these tumor indications, atezolizumab has prolonged OS and/or induced durable disease responses. Notably, similar to other ICIs, the effects of single-agent atezolizumab on PFS were modest, suggesting the possibility of delayed anticancer immune effects contributing to the observed survival benefit (Fehrenbacher et al 2016). Like other ICIs, treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs) including pneumonitis, hepatitis, colitis, endocrinopathies including hypophysitis, ocular toxicity, myocarditis, myositis, pancreatitis, and severe cutaneous adverse reactions (Michot et al 2016; Tecentriq US PI and EMA SmPC).

Immune Checkpoint Inhibitors in mCRPC

Immune checkpoint inhibitor (ICI) monotherapy with atezolizumab; the PD-1 inhibitor, pembrolizumab; the CTLA-4 inhibitor, ipilimumab; as well as the combination of the PD-1 inhibitor, nivolumab, with ipilimumab have been studied in mCRPC. Prostate cancer is often a slow-growing tumor that may allow enough time for ICI therapy to activate the immune system with higher percentages of regulatory T-cells (Tregs) being found in higher stages of prostate cancer and tumor-infiltrating cytotoxic lymphocytes expressing high levels of PD-1 (an indicator of T-cell exhaustion), among other observations (Schepisi et al 2017, Ebelt et al 2009, Sfanos et al 2009).

However, there are limited data available from ICI monotherapy trials in subjects with mCRPC. With the exception of unresectable or metastatic MSI-H or dMMR prostate cancer, single-agent pembrolizumab has failed to generate impressive RECIST responses although it has demonstrated encouraging immune responses. For example, the KEYNOTE-199 study in docetaxel-refractory mCRPC enrolled PD-L1-positive, PD-L1-negative, and bone-predominant with no measurable disease (irrespective of PD-L1 status) cohorts. Overall, 19% of 193 subjects

had any PSA reduction, while the objective response rate (ORR) was 6% and 3% for the PD-L1-positive and PD-L1-negative cohorts, respectively.

In a Phase 1 study of 15 men not preselected for PD-L1 status and with post-enzalutamide and/or post-sipuleucel-T mCRPC, atezolizumab monotherapy was associated with a median PFS of 3.4 months (95% CI: 2.3, 5.7); the 6-month PFS rate was 26.7% (95% CI: 4.3, 49.1); only one subject (9%) had a partial response (PR) per immune-related response criteria (irRC [irPR]); and only 2 subjects (13%) had an at least 50% decrease in PSA from baseline (Kim et al 2018).

Monotherapy with the CTLA-4 inhibitor, ipilimumab (10 mg/kg IV q3W for four doses and then q12W), was studied in two randomized, double-blind, placebo-controlled trials of men with mCRPC, one in men previously treated with docetaxel and the other in chemotherapy-naïve men. The primary endpoint in both studies was OS with key secondary endpoints of radiographic PFS and pain response. Neither study met its primary endpoint (Kwon et al 2014, Beer et al [J Clin Oncol] 2017). In the post-docetaxel study, median OS was numerically longer for ipilimumab compared with placebo but the HR did not reach statistical significance (11.2 vs 10.0 months, HR 0.85 [95% CI: 0.72, 1.00; p=0.053]) with subgroup analyses generally suggesting greatest benefit from ipilimumab in those subjects with good prognostic features. Median PFS was longer for ipilimumab compared with placebo (4.0 vs 3.1 months, HR 0.70 [95% CI: 0.61, 0.82]). The number of subjects meeting the prespecified criteria for a pain response was too small to allow meaningful assessment, while more ipilimumab subjects achieved a PSA reduction of at least 50% compared with placebo (13.1% vs 5.3%). In the pre-docetaxel study, the HR for OS was 1.11 (95% CI: 0.88, 1.39; p=0.37). However, median PFS was longer in the ipilimumab group compared with placebo (5.6 vs 3.8 months, HR 0.67 [95% CI: 0.55, 0.81]), as was time to nonhormonal cytotoxic chemotherapy (18.0 vs 10.9 months, HR 0.65 [95% CI: 0.52, 0.83]), which suggested activity with ipilimumab.

In the CheckMate-650 study among post-NHT mCRPC subjects, 25% (8 of 32) responded to the combination of nivolumab and ipilimumab at a median follow-up of 11.9 months. Among post-chemotherapy, post-NHT mCRPC subjects, 10% (3 of 30) had a response at a median follow-up of 13.5 months (Sharma et al 2019).

Overall, currently available data suggest that single-agent ICIs may only benefit a subset of patients with mCPRC.

1.4 Combination Therapy with Cabozantinib and Atezolizumab

Preclinical studies (Kwilas et al 2014, Lu et al 2017, Wang et al 2019) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al

2014) suggest that cabozantinib promotes an immune-permissive environment, which might lead to synergistic effects from combination treatment with ICIs, independent of PD-L1 expression.

High levels of circulating myeloid-derived suppressor cells (MDSCs), which are involved in tumor immune evasion (Gabrilovich and Nagaraj 2009), have been associated with increased PSA levels and tumor metastasis (Vuk-Pavlović et al 2010, Brusa et al 2013, Hossain et al 2015, Idorn et al 2014). In addition, high levels of immunosuppressive peripheral blood regulatory T cells (Tregs) have been identified in patients with prostate cancer and may hamper the anti-tumor response (Miller et al 2006). Preclinical studies in PTEN/p53 deficient mice treated with cabozantinib showed rapid elimination of invasive prostate cancer through a neutrophil-mediated anticancer innate immune response (Patnaik et al 2017).

In a chimeric murine model of mCRPC, anti-CTLA-4 or anti-PD-1 antibodies had a modest effect on tumor mass, but in combination with cabozantinib, a strong synergistic response mediated by neutralization of MDSCs (CD11b+, Gr1+) was observed (Lu et al 2017). Cabozantinib inhibited PI3K signaling, which impaired the release of cytokines by prostate cancer cells; the cytokines in turn induced expression of MDSC genes responsible for tumor suppressive activity. Inhibitory modulation of Gr1+ MDSCs was associated with an increase in CD8+ T cell tumor infiltration in prostate tumors, which supports the antagonistic activity of Gr1+ MDSCs on the CD8+ population of T cells. The collective preclinical evidence supports the combination of cabozantinib with atezolizumab as a therapeutic strategy for CRPC.

COSMIC-021 is an ongoing Phase 1b study that evaluates the efficacy of cabozantinib in combination with atezolizumab in multiple tumor types including subjects with metastatic CRPC without small-cell features who have radiographically progressed in soft tissue on or after NHT (enzalutamide and/or abiraterone) initiated for treatment of metastatic disease. Subjects are required to have measurable soft tissue (visceral or adenopathic) disease per RECIST 1.1. Prior treatment with docetaxel is only permitted when given in combination with ADT for metastatic castration-sensitive prostate cancer prior to treatment with NHT. Subjects receive cabozantinib 40 mg po qd and atezolizumab 1200 mg intravenously IV q3w. As of 21 October 2019, 61 CRPC subjects had been enrolled in this study and 44 of these subjects with at least 12 weeks of follow-up were evaluable for response. Fourteen of the 44 evaluable subjects (31.8%) had a confirmed tumor response per RECIST 1.1 by Investigator assessment, including 2 subjects with a complete response and 12 with partial response. Disease control rate was 80%. An additional subject, not included as responder above, with initial PD per RECIST 1.1 exhibited a durable irPR per irRECIST criteria. An objective tumor response rate was also observed (33%) in 36 patients with features of disease associated with poor prognosis: measurable visceral disease and/or measurable extrapelvic lymph node metastasis. The observed clinical activity of the

combination therapy in COSMIC-021 is especially encouraging given the more limited single-agent activity of either cabozantinib or atezolizumab in subjects with metastatic CRPC and is suggestive of cooperative effects of these agents (Schoffski et al 2017, Kim et al 2018).

To date, AEs observed within XL184-021 mCRPC Cohort 6 have been consistent with the safety profile of cabozantinib and atezolizumab. As of 21 October 2019, of the 44 subjects described above, 42 (95%) experienced at least one AE. Forty-one (93%) subjects experienced at least one related AE, 28 (64%) at least one Grade 3 or 4 AE, 28 (64%) at least one related Grade 3 AE, two (4.5%) a Grade 4 AE (pulmonary embolism [not related], diverticular perforation [related), and one (2%) a related Grade 5 AE (dehydration).

Among these 44 subjects, the most frequent AEs (reported in ≥ 10% of subjects) observed as of the 21 October 2019 data cutoff, regardless of causality, were fatigue (57%), nausea (48%), decreased appetite (45%), diarrhea (39%), palmar-plantar erythrodysesthesia syndrome (32%), vomiting (32%), aspartate aminotransferase increased (30%), dysgeusia (30%), headache (30%), alanine aminotransferase increased (25%), hyponatremia (25%), cough (23%), weight decreased (20%), abdominal pain (18%), anemia (18%), arthralgia (18%), constipation (18%), dizziness (18%), platelet count decreased (18%), pulmonary embolism (18%), dysphonia (16%), hypertension (16%), hypophosphatemia (16%), blood alkaline phosphatase increased (14%), dry mouth (14%), hyperglycemia (14%), peripheral edema (14%), rash maculo-papular (14%), stomatitis (14%), white blood cell count decreased (14%), dehydration (11%), fall (11%), gamma-glutamyltransferase increased (11%), lymphocyte count decreased (11%), neutrophil count decreased (11%), oral pain (11%), and sinusitis (11%). Of note, the majority of pulmonary embolism events with accompanying narratives (ie, serious events) were discovered incidentally on restaging CT scans: 6 of 7 (85.7%) described asymptomatic clinical courses. All 6 subjects experiencing an incidental event continued on cabozantinib after a brief interruption and initiation of anticoagulation. Immune-related AEs (irAEs) were also observed.

Seven (16%) subjects discontinued all study treatment (both cabozantinib and atezolizumab) due to an AE or serious adverse event (SAE) unrelated to disease progression. Four (9.1%) subjects discontinued all study treatment due to an AE or SAE related to disease progression.

Adverse events were managed with dose modifications and supportive care. The overall safety profile is consistent with what has been observed with each agent individually. The lower dose of cabozantinib (40 mg), even in combination with atezolizumab, appears to be better tolerated than the 60 mg single agent cabozantinib dosing regimen used in the earlier COMET-1 trial in mCRPC. In that study, 33% of subjects discontinued cabozantinib due to an AE, and 88% had a dose modification. Median duration of treatment was 20 weeks.

Overall, the combination of cabozantinib and atezolizumab showed acceptable tolerability and encouraging clinical activity in this patient population, particularly given the poor prognosis and limited treatment options. For further information on COSMIC-021, refer to the current cabozantinib Investigator's Brochure.

1.5 Rationale

1.5.1 Rationale for Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic Castration-Resistant Prostate Cancer

Preclinical studies and clinical observations suggest that cabozantinib promotes an immune-permissive environment, which might lead to synergistic effects from combination treatment with ICIs (Section 1.4). In Cohort 6 of the ongoing Phase 1b study XL184-021, the combination of cabozantinib and atezolizumab showed encouraging clinical activity and acceptable tolerability in mCRPC subjects who had radiographically progressed in soft tissue on or after NHT (enzalutamide and/or abiraterone) treatment (Section 1.4).

There is a significant unmet medical need for treatment options for men with mCRPC who have previously received an NHT for mCRPC and/or earlier lines of disease (mCSPC [including locally advanced M0 CSPC], M0 CRPC) and who have measurable visceral disease or measurable extrapelvic adenopathy. Based on the encouraging data from Cohort 6 of Study XL184-021, the current Phase 3 study will evaluate the safety and efficacy of cabozantinib in combination with atezolizumab versus a second NHT in subjects with such mCRPC who biochemically or radiographically progressed on that NHT. Furthermore, this study is particularly suited to men with a good performance status who wish to avoid chemotherapy or to men deemed unable to tolerate side effects from chemotherapy.

1.5.2 Rationale for Study Design

1.5.2.1 Rationale for Patient Population

This is a randomized, open-label, controlled Phase 3 study of cabozantinib in combination with atezolizumab versus a second NHT in subjects with mCRPC who have previously received one, and only one, NHT for mCRPC and/or earlier lines of disease (mCSPC [including locally advanced M0 CSPC] or M0 CRPC), who biochemically or radiographically progressed on that NHT, and who have measurable visceral disease or measurable extrapelvic adenopathy. The selection of subjects with measurable visceral disease or measurable extrapelvic adenopathy is based on review of data from Cohort 6 in the XL184-021 study (Section 1.4).

A meta-analysis of the impact of metastatic site on overall survival in nearly 9000 men enrolled in nine Phase 3 trials of docetaxel in previously chemotherapy-naïve men with mCRPC showed

that visceral disease is associated with a poor prognosis, with liver disease associated with a median OS of 13.5 months and lung disease with 19.5 months (Halabi et al 2016). In the post-chemotherapy AFFIRM (enzalutamide) and COUGAR-301 (abiraterone) mCRPC NHT trials, 23.2% (278/1199) and 29.5% (352/1195) of subjects had visceral (ie, liver, lung) disease at baseline, respectively (Goodman et al 2014, Loriot et al 2017). Visceral disease (12%; 204/1717) was also documented in the pre-chemotherapy mCRPC PREVAIL trial of enzalutamide (Alumkal et al 2017; visceral disease was not permitted in the sister COUGAR-302 study of abiraterone). Thus, visceral disease is common in mCRPC. Furthermore, the proportion of men with mCRPC with measurable disease may be increasing due to the increased sensitivity of currently available imaging modalities and, possibly, the increasing use of docetaxel and novel hormonal therapies in subjects before they even reach the mCRPC state.

Subjects will be stratified by presence or absence of liver metastasis, a particularly adverse prognostic factor for survival in patients with visceral disease enrolled in mCRPC trials (Pond et al 2014). In addition, they will be stratified by whether they had previously received docetaxel for locally advanced or metastatic castration-sensitive prostate cancer (yes/no) had their mCRPC been preceded by documented locally advanced or metastatic CSPC (response is "no" if subject previously had M0 CRPC). As docetaxel treatment is now thought to be used in approximately 25% of newly diagnosed mCSPC patients with primarily high-volume disease (CHAARTED; Sweeney et al 2015), this stratification may decrease bias in efficacy analyses given high-volume disease's representing another adverse prognostic factor. Furthermore, stratification on use of docetaxel for locally advanced or metastatic CSPC (including locally advanced M0 CSPC) may reduce bias in OS assessment across the study arms, as taxane treatment prior to mCRPC could reduce the efficacy of taxane treatment initiated after subjects progress on study drug(s) and could be used following discontinuation of study treatment. Finally, subjects will be stratified on whether their first NHT was given for first-line treatment of mCRPC, M0 CRPC or mCSPC (including locally advanced M0 CSPC), as the survival experience for subjects meeting entry criteria could differ by disease state when the first NHT was given.

1.5.2.2 Rationale for Multiple-Primary Endpoints

The multiple-primary endpoints in this study are PFS per RECIST 1.1 evaluated by a Blinded Independent Radiology Committee (BIRC), and OS. OS has long served as a primary endpoint in multiple mCRPC trials, but PFS is also a clinically relevant primary endpoint supported by regulatory precedent in advanced prostate cancer trials (eg, PREVAIL, COUGAR-302, TALAPRO-2, LATITUDE, ARCHES, TITAN).

Inclusion of PFS in soft tissue per RECIST 1.1 criteria as a multiple primary endpoint is supported by the observation that RECIST changes are associated with survival in men who

participated in the docetaxel control arm of Phase 3 mCRPC trials. For instance, in the VENICE trial, the OS HR was 0.64 (95% CI: 0.42, 0.99) for those who had a PR compared with those without such a response, and 1.78 (95% CI: 1.07, 2.95) for those with progressive disease (PD) compared to those without PD. Similarly, in the MAINSAIL trial, the corresponding OS HRs were 0.51 (95% CI: 0.22, 1.18) and 3.51 (95% CI: 1.92, 6.43), respectively (Sonpavde et al 2016). Furthermore, in SWOG study S0421, the median OS was 7.1 (95% CI: 3.5, 8.8), 13.4 (95% CI: 11.4 15.6), and 16.3 (95% CI: 10.0, 19.6) months for men with PD, stable disease (SD), and unconfirmed partial response (uPR), respectively; in a multivariate model, the OS HR was 2.47 (95% CI: 1.42, 4.29) for those with PD compared with those with uPR (Sonpavde et al 2017). Interestingly, in a review of 31 Phase 3 mCRPC trials that included men with measurable disease, preceding objective tumor responses in Phase 2 studies best correlated with positive OS data in Phase 3 in the pre-chemotherapy setting, but less so in 1) post-chemotherapy studies, where response rates were lower and OS shorter, and 2) studies that combined docetaxel with another agent, where there have been no successful trials (Brown et al 2018). Therefore, it is reasonable to employ PFS per RECIST 1.1 as a multiple primary endpoint in mCRPC, with the expectation that, at the time of the primary PFS analysis, no detriment to OS should be demonstrated.

Additionally, the inclusion of PFS per RECIST 1.1 rather than per Prostate Cancer Working Group 3 (PCWG3) as a multiple primary endpoint is supported by the objective of isolating the primary radiographic evaluation to soft tissue given the key requirement for measurable soft tissue disease at screening as a driver of high risk. Of note, in a posthoc subgroup analysis of subjects with visceral disease enrolled in COMET-1, a PFS benefit associated with cabozantinib treatment was observed regardless of whether bone scan data (showing two or more new lesions not consistent with tumor flare) informed the PFS endpoint (Table 1-1), adding further support for using PFS per RECIST 1.1 as a multiple primary endpoint. It is generally recognized that bone scans are not highly sensitive means of detecting bone metastases and bone disease progression. The significantly higher likelihood that radiographic progression may be seen in visceral disease (per RECIST 1.1) compared with contemporaneous bone disease (per PCWG) further justifies PFS per RECIST 1.1 as a multiple primary endpoint.

Finally, the current trial landscape for men with mCRPC now includes combination of ICIs with each of chemotherapy, NHTs (eg, atezolizumab plus enzalutamide, pembrolizumab plus enzalutamide), or PARP inhibitors; lutetium-177 PSMA617; and other novel research treatments, which may render the ability to demonstrate an effect on OS challenging as patients switch to new systemic therapies upon radiographic progression.

The proposed trial is therefore designed to provide statistically robust evaluations of PFS and OS as multiple primary endpoints. PFS will be assessed by a BIRC to reduce potential bias in this open-label study.

1.5.2.3 Rationale for Control Arm

Treatment with a second NHT (as approved standard of care) after failure of a first NHT initiated to treat mCRPC leads to a PSA response in approximately 20% of patients (Azad et al 2015, Suzman et al 2014, Matsubara et al 2018, Maughan et al 2017, Khalaf et al 2018). Given that subjects may, among others, receive either abiraterone or enzalutamide as the first NHT, the proposed control arm includes both agents to afford subjects the opportunity to receive the other. Subjects who have received another NHT, such as apalutamide or darolutamide, could receive either abiraterone with prednisone, or enzalutamide (Investigator's choice). Given an assumed median OS of 14 months for the control group, a projected median PFS of 4 months affords the opportunity for subjects in the control group to initiate taxane-based or new investigational therapy should progression occur under trial treatment.

Given that many men with mCRPC may wish to avoid chemotherapy or may be deemed unable to tolerate side effects from chemotherapy, alternative therapies are preferred in this disease stage setting. This is supported by the absence of any published evidence in the population to be enrolled in this study that taxane-based therapy (eg, docetaxel or cabazitaxel) is more efficacious than a second NHT after prior treatment with a first NHT (Suzman et al 2014, Schweizer et al 2014, Aggarwal et al 2014, Azad et al 2014, Mezynski et al 2012). This observation is consistent with the hypothesis that docetaxel's effect is mediated, at least in part, by disruption of microtubule function relevant to proper AR function. Review of this literature, which included studies in which the percentage of patients with visceral disease ranged from 6% to 48%, showed that the median OS was approximately 12 months, and the median PFS approximately 4 months, similar to what was seen in studies of chemotherapy-naïve patients who received a second NHT after a first NHT. Restricting the control treatment to second NHT also avoids the potential for serious chemotherapy-related toxicity (eg, myelosuppression, febrile neutropenia, neuropathy, alopecia, etc).

1.5.3 Rationale for Study Treatment Dose Selection and Treatment Schedule

In accordance with the standard approved dose, atezolizumab 1200 mg will be administered as an IV infusion over 60 min (± 15 min) every 3 weeks (-2 days) on Day 1 of each 21-day cycle. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes (Tecentriq US PI, SmPC).

In the Phase Ib study, a total of 12 subjects with advanced RCC were evaluated in the dose-escalation stage at the 40-mg or 60-mg cabozantinib dose levels (six subjects each) plus the standard dose of atezolizumab. After reviewing all available safety and efficacy data of the dose-escalation stage, the Cohort Review Committee determined that cabozantinib 40 mg qd orally in combination with 1200 mg atezolizumab q3w IV is the recommended dose for the expansion-stage combination-therapy cohorts. The Cohort Review Committee decision was based on the favorable safety profile of the 40-mg cabozantinib dose level over a prolonged time on study treatment with less frequent dose reductions and encouraging preliminary efficacy, which was deemed to optimize the benefit/risk of the combination therapy in multiple solid tumor expansion cohorts including CRPC cohorts.

Encouraging and durable responses were observed in the XL184-021 CRPC Expansion Stage Cohort 6, and data from which informed the definition of the population for this proposed study (Section 1.4). Furthermore, the combination of cabozantinib and atezolizumab has been tolerable, and the safety profile has been consistent with that of each agent individually.

The lower 40-mg dose of cabozantinib in combination with atezolizumab is further supported by an exposure-response analysis of safety and efficacy endpoints from cabozantinib monotherapy data in the METEOR trial in second-line RCC evaluating 60-mg cabozantinib versus everolimus (Lacy et al 2018). Dose reductions to 40 mg and then 20 mg were allowed and occurred in 62% of patients in the cabozantinib group. The 60-mg exposure was associated with a higher risk for selected adverse events PPE (≥ Grade 1), fatigue/asthenia (≥ Grade 3), hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg) and diarrhea (≥ Grade 3) with predicted HRs of 1.49, 1.42, 1.36, and 1.33, respectively, relative to the predicted average steady-state cabozantinib concentration for a 40-mg starting dose. While the efficacy was predicted to be somewhat lower with a 40-mg monotherapy dose compared to the 60-mg dose (higher risk of disease progression/death (HR = 1.1), lower maximal median reduction in tumor size (-9.1% vs. –11.9%) and lower ORR (15.6 % vs. 19.1%), the benefit/risk in combination with atezolizumab based on the dose-escalation stage of the COSMIC-021 Phase Ib study favored the lower 40-mg cabozantinib dose, considering the potential overlapping adverse events of the two agents.

The dosing regimens for abiraterone with prednisone and enzalutamide are based on their respective labeling in the US, Europe, and other regions.

An open-label design takes into consideration the impracticality of blinding given the desire to avoid dummy infusions in the control arm, in addition to the complications related to abiraterone administration with twice daily prednisone, a requirement that does not exist for enzalutamide.

1.6 Overall Risk Benefit Assessment

Prostate cancer is the most common cancer among men worldwide and the second leading cause of cancer deaths in the US (Bashir 2015), where its incidence in 2018 exceeded that of cancers of the bladder, kidney and testis combined (NIH NCI SEER 2018).

The incidence of visceral metastases in men with mCRPC may be increasing and is associated with a particularly poor prognosis, particularly in the setting of liver disease (Nafissi et al 2019, Iwamoto et al 2018, Pezaro et al 2014, Whitney et al 2017).

In Cohort 6 of the ongoing Phase 1b Study XL184-021, the combination of cabozantinib with atezolizumab has demonstrated encouraging clinical activity, indicating possible cooperative effects, based on previous data on the contribution of single components (Sections 1.2 and 1.3), of these agents in subjects with mCRPC who have previously received an NHT for metastatic disease and who have measurable visceral disease or measurable extrapelvic adenopathy. Furthermore, the combination of cabozantinib and atezolizumab has been well-tolerated, and the safety profile has been consistent with that of each agent individually.

Study inclusion/exclusion criteria were designed to prevent subjects at a heightened safety risk from entering the study (Section 4.2 and Section 4.3). The protocol provides guidance to Investigators for the management of important AEs that are associated with cabozantinib (Section 6.6.1), atezolizumab (Section 6.6.2), abiraterone with prednisone (Section 6.6.3), and enzalutamide (Section 6.6.4). Frequent safety assessments including laboratory assessments will allow identification and early intervention of potential AEs due to study treatment.

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

The safety profile of each agent is well defined, and dose modification guidelines have been established and used in previous clinical studies to effectively manage side effects. Therefore,

potential benefits of evaluating the combination of these agents in this patient population outweigh the potential risks.

1.7 Study Conduct

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

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

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

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

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objective

The primary objective of this study is to evaluate the efficacy of cabozantinib in combination with atezolizumab versus second NHT (abiraterone or enzalutamide) in subjects with mCRPC who have previously received one and only one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat mCSPC (including locally advanced M0 CSPC), M0 CRPC, and/or mCRPC where biochemical progression (PSA progression) or radiographic progression has occurred on that NHT, and who have measurable visceral disease or measurable extrapelvic adenopathy.

2.2 Endpoints

Multiple-primary efficacy endpoints:

- Duration of PFS per RECIST 1.1 per BIRC
- Duration of OS

Secondary efficacy endpoint:

- ORR per RECIST 1.1 per BIRC

Additional endpoints:

- PSA response rate
- Duration of radiographic response per RECIST 1.1 (per Investigator and BIRC)
- Duration of PFS per PCWG3 per BIRC
- Time to PSA progression
- Time to SSE
- Time to pain progression
- Time to chemotherapy
- Health care resource utilization
- Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health as assessed by the EuroQol Health questionnaire EQ-5D-5L and European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30
- Safety as assessed through the evaluation of adverse events (AEs), including immune-related adverse events (irAEs)
- Pharmacokinetics (PK) of cabozantinib given in combination with atezolizumab
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Correlation of immune cell, tumor cell, and plasma biomarker analyses with clinical outcomes

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted at approximately 280 sites.

3.2 Estimated Study Dates and Duration of Subject Participation

It is estimated that approximately 24 months will be required to randomize 580 subjects. The number of events required for the primary analyses of PFS (202 events among the first 324 randomized subjects) and OS (340 events among all 580 randomized subjects) is expected to

be observed approximately 21 months and 37 months (final OS analysis), respectively, after the first subject is randomized. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. These estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation.

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

3.3 Overview of Study Design

This is a Phase 3, multicenter, randomized, parallel group, open-label, controlled trial of the combination of cabozantinib (40 mg qd) with atezolizumab (1200 mg IV q3W) versus second NHT (abiraterone or enzalutamide) in subjects with mCRPC (adenocarcinoma) who previously received one and only one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat mCSPC (including locally advanced M0 CSPC), M0 CRPC, and/or mCRPC. PFS and OS are the multiple-primary endpoints. The primary analysis of PFS will be based upon RECIST 1.1 per BIRC assessment. Approximately 580 eligible subjects who have mCRPC with measurable visceral metastasis or measurable extrapelvic lymphadenopathy, and whose disease is deemed to be worsening based on PSA or radiographic soft tissue progression in the opinion of the Investigator, will be randomized at approximately 280 sites in this trial.

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

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

Each subject's course of trial participation will consist of the following periods:

Pre-Treatment Period: Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying screening assessments must be performed within 21 days before randomization unless otherwise specified. If there is a change in clinical status after screening and prior to randomization, these assessments are to be repeated as clinically indicated. Prior to randomization, the Investigator will designate in the interactive response technology (IRT) system the NHT (abiraterone, apalutamide, darolutamide, or enzalutamide) the patient previously received and progressed on. If eligible and randomized to the control group (second

NHT), the IRT system will then dispense enzalutamide if the prior NHT was abiraterone; abiraterone if the prior NHT was enzalutamide; and Investigator's choice of abiraterone or enzalutamide if the prior NHT was apalutamide or darolutamide.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to cabozantinib plus atezolizumab or second NHT, respectively. Based on treatment assignment, subjects will begin treatment on one of the following regimens:

Experimental Arm (290 subjects):

Cabozantinib (40 mg po qd) plus atezolizumab (1200 mg IV q3w)

Control Arm (290 subjects):

Abiraterone (1000 mg po qd) + prednisone (5 mg po bid), OR enzalutamide (160 mg po qd)

Details about the study treatment regimens are provided in Section 6.

Subjects may receive study treatment, even after protocol-defined progression, until they are no longer clinically benefitting in the opinion of the Investigator, unless they 1) need subsequent systemic anticancer treatment or urgent tumor-directed alternative medical intervention (eg, to central nervous system [CNS] metastases), 2) experience unacceptable toxicity, or 3) have any other reason for treatment discontinuation as listed in the protocol (Section 3.5). In the absence of such, continued treatment after radiographic progression may occur in subjects who meet both of the following criteria:

- Clinical benefit per Investigator judgment
- ECOG performance status 0 or 1

Crossover among treatment arms will not be allowed.

Post-Treatment Period: A first Post-Treatment Follow-up Visit (FU-1) for safety assessment is to occur at least 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Radiographic tumor, PSA, pain, and health-related quality of life (HRQOL) assessments are to continue, regardless of whether study treatment is given, reduced, held, or discontinued until a criterion for ending radiographic

assessments is met (Section 5.6.6). Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

In addition, subjects are to be contacted every 8 weeks (± 7 days) after FU-2 to assess survival status and document receipt of nonprotocol anticancer therapy (NPACT). This will continue until the subject expires or the Sponsor decides to discontinue collection of these data in the study. Every effort must be made to collect these protocol-specified evaluations unless consent to provide these data is withdrawn.

Study Completion: The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS in any of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results).

Maintenance Phase/Treatment After Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes to have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented.

In the Maintenance Phase, subjects on study treatment will continue to receive the study treatment(s) to which they were randomized until they meet a protocol-defined criterion for treatment discontinuation. Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests, ECGs, symptom-directed physical examination and vital signs) and tumor assessments every 12 weeks (or more frequently as clinically indicated) for as long as they are in this phase.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of serious adverse events (SAEs), certain AEs (including AEs of special interest [AESIs, Table 8-1; whether serious or not] and AEs leading to dose modifications or treatment discontinuation), and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

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

3.4 Treatment Groups and Randomization

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

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

- **Experimental Arm** (290 subjects):
  Cabozantinib (40 mg po qd) plus atezolizumab (1200 mg IV q3w)
- **Control Arm** (290 subjects):
  Abiraterone (1000 mg po qd) + prednisone (5 mg po bid), OR enzalutamide (160 mg po qd)

Details about treatment regimens are provided in Section 6.

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

- Liver metastasis (yes/no)
- Prior docetaxel for locally advanced or metastatic castration-sensitive prostate cancer (yes/no)
    - Response is "no" if subject previously had M0 CRPC
- First NHT given for mCRPC vs M0 CRPC vs metastatic castration-sensitive prostate cancer. Note: For subjects who have received the same NHT for both mCRPC and either mCSPC (including locally advanced M0 CSPC) or M0 CRPC, subjects should be stratified by the disease state for which they received their first NHT even if they did not progress on it then.

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

3.5 Treatment Discontinuation and Withdrawals

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

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

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

3.5.1 Treatment Discontinuation

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

Furthermore, any of the following conditions require discontinuation of study treatment:

- Subject no longer experiences clinical benefit as determined by the Investigator
- Unacceptable side effects the Investigator feels may be due to study treatment
- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention
- Necessity for treatment with non-protocol systemic anticancer therapy or urgent tumor-directed alternative medical intervention (eg, to CNS metastases)
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment related AEs unless approved by the Sponsor. (Note: temporary interruptions of study treatment for greater than 12 weeks due to the effects of COVID-19 and unrelated to AEs are described in Appendix N)
- Refusal of sexually active fertile subjects to use highly effective methods of contraception (defined in Appendix E)
- Significant noncompliance with the protocol schedule in the opinion of the Investigator or the Sponsor

In addition, specific criteria for discontinuation are provided for cabozantinib and atezolizumab (Sections 6.6.1 and 6.6.2, respectively), abiraterone plus prednisone (Section 6.6.3), and enzalutamide (Section 6.6.4).

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

For subjects who discontinue study treatment, every effort must be made to undertake protocol-specified follow up procedures including end of treatment assessments, survival follow-up, and documentation of subsequent anticancer treatment(s) unless consent for non-interventional study assessments is also withdrawn.

If a subject is discontinued from study treatment because of an AE (including AESI; Table 8-1) considered to be related to study treatment, the event must be followed until resolution or determination by the Investigator that the event has become stable or irreversible.

3.5.2 Study Withdrawal

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

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

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

3.5.3 Study Completion

The study will be complete if the null hypothesis is rejected for the primary endpoint of OS in any of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results).

3.5.4 End of Trial

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

4 STUDY POPULATION

4.1 Target Population

This study will enroll subjects with mCRPC who have previously received one, and only one, NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat mCSPC (including locally advanced M0 CSPC), M0 CRPC, and/or mCRPC, and who have measurable visceral disease (eg, adrenal, kidney, liver, lung, pancreas, spleen; but not bladder or other pelvic structures) or measurable extrapelvic adenopathy. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that subjects fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

4.2 Inclusion Criteria

1. Men with histologically or cytologically confirmed adenocarcinoma of the prostate.

   Note: Neuroendocrine differentiation and other histological features are permitted if adenocarcinoma is the primary histology.

2. Subjects must have had a rising PSA or radiographically progressed on their prior treatment with one, and only one, NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) for castration-sensitive locally advanced (T3 or T4) or metastatic castration-sensitive prostate cancer, M0 CRPC, and/or mCRPC.

   Note: Subjects may have previously received taxane-based chemotherapy for locally advanced or metastatic castration-sensitive prostate cancer but no other approved or experimental nonhormonal systemic therapies for mCRPC.

3. Bilateral orchiectomy or ongoing ADT with a gonadotropin-releasing hormone (GnRH) agonist/antagonist (surgical or medical castration), with serum testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening.

4. Measurable (extrapelvic soft tissue) metastatic disease per Investigator assessment as defined by at least one of the following:

   a. Measurable visceral (eg, adrenal, kidney, liver, lung, pancreas, spleen) disease per RECIST 1.1, OR

   b. Measurable extrapelvic adenopathy (ie, adenopathy above the aortic bifurcation).

5. Progressive disease at study entry as defined by at least one of the following two criteria:

   a. Prostate specific antigen (PSA) progression defined by a minimum of 2 rising PSA values from 3 or 4 most recent consecutive assessments with an interval of at least 7 days between assessments.

      Note: If qualifying solely by PSA progression, the screening PSA value must be at least 2 ng/mL (2 µg/L), and the oldest qualifying value must have been based on a blood sample drawn no longer than one year prior to signing of the informed consent form (ICF); up to one PSA decrease is permitted as long as it is not the most recent

value. If the study lab is the local lab at which the subject's previous PSA blood samples were drawn, then the screening local lab PSA must be the highest, OR

b. Soft tissue disease progression (PD) in the opinion of the Investigator.

Note: Subjects with bone disease progression alone are not eligible.

6. Age ≥ 18 years old or meeting country definition of adult, whichever is older, on the day of consent.
7. ECOG performance status score of 0 or 1.
8. Recovery to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy in the opinion of the Investigator.
9. Adequate organ and marrow function, based upon all of the following laboratory assessments from samples obtained within 21 days before randomization:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 × 10^9/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. Platelets ≥ 100,000/mm^3 (≥ 100 × 10^9/L) without transfusion within 2 weeks before screening laboratory sample collection.
    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 1 week before screening laboratory sample collection.
    d. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN)

    Note: Subjects with known Gilbert's disease or unconjugated hyperbilirubinemia who have serum bilirubin level ≤ 3 × ULN may be enrolled.

    e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both ≤ 3 × ULN. Subjects with known hepatic metastasis may enroll with serum ALT and AST both ≤ 5 × ULN.
    f. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation: (140 – age) × weight (kg)/(serum creatinine [mg/dL] × 72).
    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g.
    h. Negative hepatitis B surface antigen (HBsAg) test
    i. Negative hepatitis C virus (HCV) antibody test, or positive HCV antibody test followed by a negative HCV RNA test and no ongoing anti-HCV therapy.

    Note: The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

10. Understanding and ability to comply with the protocol requirements, including scheduled visits, treatment plan, laboratory tests, and all other study procedures. Evidence of a signed and dated ICF, indicating that the subject has been informed of all pertinent aspects of the

study, prior to any screening assessments except those procedures performed as standard of care within the screening window.

11. Sexually active fertile subjects and their female partners must agree to use highly effective methods of contraception during the course of the study and for 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm). A barrier contraceptive method (eg, condom) is also required. In addition, men must agree not to donate sperm during these same periods.

4.3 Exclusion Criteria

1. Only evidence of metastasis is adenopathy below the aortic bifurcation, non-measurable soft tissue (visceral or adenopathic) disease per RECIST 1.1, or bone-only disease.
2. Any prior systemic nonhormonal therapy initiated for the treatment of mCRPC.
3. Receipt of abiraterone within 1 week; cyproterone within 10 days; or receipt of flutamide, nilutamide, bicalutamide, enzalutamide, or other androgen-receptor inhibitors within 2 weeks before randomization.

   Note: Subjects receiving prior enzalutamide, bicalutamide, flutamide, or nilutamide monotherapy without ADT at the time of screening are not eligible, unless bilateral orchiectomy has already been performed.
4. Radiation therapy within 4 weeks (2 weeks for bone metastases) prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
5. Known brain metastases (symptomatic or non-symptomatic) or cranial epidural disease unless adequately treated with radiotherapy, radiosurgery, or major surgery (eg, removal or biopsy of brain metastasis) and clinically stable for at least 4 weeks prior to randomization. *Note: Subjects who are neurologically symptomatic as a result of their CNS disease or receiving systemic corticosteroid treatment for their CNS disease are not eligible.*
6. Symptomatic or impending spinal cord compression or cauda equina syndrome.
7. Concomitant anticoagulation with oral anticoagulants including, but not limited to, platelet inhibitors (eg, clopidogrel or ticagrelor), warfarin, dabigatran, and betrixaban, except for those specified below.
    a. Allowed anticoagulants are:
        i. Prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
        ii. Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before randomization and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

8. Administration of a live, attenuated vaccine within 30 days prior to randomization. The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.
9. Systemic treatment with, or any condition requiring, either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to randomization. Subjects with brain metastases requiring systemic corticosteroid at any dose are not eligible.

   Note: Prednisone (5 mg po bid) should be used with abiraterone. Inhaled, intranasal, intra-articular, and topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease (eg, in presence of adrenal metastasis). Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.
10. Uncontrolled, significant intercurrent or recent illness that may impede interpretation of safety data, including, but not limited to, the following conditions:
    a. Cardiovascular and cardiac disorders:
       i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, torsades de pointes) within 6 months before randomization
       ii. Uncontrolled hypertension defined as systolic blood pressure (BP) > 150 mm Hg or diastolic BP > 90 mm Hg despite optimal antihypertensive treatment
       iii. Stroke, transient ischemic attack [TIA], myocardial infarction, or other symptomatic ischemic event or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism [DVT/PE]) within 6 months before randomization.

            Notes:

            Upon Sponsor approval, subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if asymptomatic and stable at screening and treated with LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban for at least 1 week before randomization.

            Non-symptomatic white matter disease in the brain is acceptable.
       iv. History of additional significant risk factors for torsades de pointes (eg, long QT syndrome)
    b. Neuropsychiatric disorder (including active suicidal ideation) likely to interfere with ability to give informed consent or comply with protocol requirements.
    c. Gastrointestinal (GI) disorders, including those affecting absorption or associated with a high risk of perforation or fistula formation:
       i. 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 (eg, Crohn's disease, ulcerative colitis)

ii. Abdominal fistula, bowel obstruction, GI perforation, or intra-abdominal abscess within 6 months before randomization

Note: Subjects with intra-abdominal abscesses are eligible if complete healing has been confirmed before randomization.

d. Hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, clinically significant hematuria, hematemesis, coagulopathy, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.

e. Known cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

f. Lesions invading major pulmonary blood vessels.

g. Other clinically significant disorders, such as:

i. Any active, known or suspected autoimmune disease (see Appendix F for a comprehensive list of autoimmune diseases and immune deficiencies).

Note: Subjects with type I diabetes mellitus, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

ii. Any active infection requiring systemic treatment.

Note: Subjects receiving oral (including prophylactic) antibiotics with no symptoms of infection at randomization or oral valacyclovir (valaciclovir) are eligible.

iii. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

Note: HIV testing will be performed at screening if and as required by local regulation.

iv. Active tuberculosis.

v. Known history of COVID-19 unless the subject has demonstrated recovery from the disease at least 30 days prior to randomization.

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

vii. Serious non-healing wound/ulcer/bone fracture per Investigator judgment.

viii. Clinically significant malabsorption syndrome per Investigator judgment.

ix. Pharmacologically uncompensated, symptomatic hypothyroidism.

Note: Asymptomatic hypothyroidism only requiring hormone replacement is allowed.

x. Moderate to severe hepatic impairment (Child-Pugh B or C) or known cirrhosis.

xi. Requirement for hemodialysis or peritoneal dialysis.

xii. History of solid organ transplantation

xiii. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

-Patients with indwelling cathethers (e.g. PleurX®) are allowed

11. Major surgery (eg, prostatectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks prior to randomization. Minor surgeries (eg, fine-needle biopsy) within 10 days prior to randomization. Subjects must have complete wound healing from major surgery or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
12. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 21 days before randomization.

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

    Note: This requirement does not apply if the subject has a permanent cardiac pacemaker in place or a history of asymptomatic bundle branch block in the absence of cardiac ischemia.
13. Inability or unwillingness to swallow tablets or receive IV administration.
14. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe infusion-related reactions to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.
15. Any other active malignancy at time of randomization or diagnosis of another malignancy within 2 years prior to randomization that requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, or carcinoma in situ of the breast.

5 STUDY ASSESSMENTS AND PROCEDURES

This protocol generally presents scheduled timelines for study procedures that will be performed based on routine safety visits (RSVs). Routine Safety Visit 1 (RSV1) is to occur no more than 72 hours prior to the first dose of any study treatment. First dose of study treatment(s) is to occur within 3 days after the date of randomization.

After RSV1, subsequent RSVs are required at least every 3 weeks (± 3 days) (ie, no more than 3 weeks [± 3 days] apart). If there is a dose delay for any study treatment, subjects must return to the site for an RSV at least every 3 weeks (± 3 days) during the dose delay and follow up with additional unscheduled visits or telephone calls weekly (or more frequently) as clinically

indicated to monitor subject safety and appropriateness for resumption of study treatment. See Appendix B for the schedule of safety assessments performed at each RSV.

In the experimental arm, an RSV is required within 72 hours prior to each planned infusion of atezolizumab (vital signs must be assessed within 60 min prior to initiation of the infusion), even if fewer than 3 weeks have elapsed since the last RSV. Once atezolizumab is restarted after a treatment delay, RSVs are to occur at least every 3 weeks (± 3 days) thereafter (ie, RSV schedule resets on date of infusion).

Radiographic tumor, PSA, HRQOL, and pain assessments are to be performed at protocol-defined intervals based on the date of randomization; all subsequent time points for these assessments will occur at a defined time interval and will not be modified as a result of modifications or discontinuations of treatment administration. Tumor assessments after randomization are to be performed every 9 weeks (± 7 days) through Week 28 (ie, the first three on-study tumor assessments) and then every 12 weeks (± 7 days; see Section 5.6.6.1). After RSV1, PSA, HRQOL, and pain assessments will occur with scheduled radiographic tumor assessments. See Sections 5.6.7, 5.6.8, and 5.6.9, respectively, for details.

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

Unscheduled visits for safety evaluations are allowed at any time (see Section 5.5).

See Appendix B for the schedule of assessments.

5.1 Pre-Treatment Period

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

To determine subject eligibility as stipulated in Section 4, subjects will undergo required screening evaluations as outlined in Appendix A and described in Section 5.6. Qualifying screening assessments must be performed within 21 days before randomization unless otherwise

stated. If there is a change in clinical status after screening and prior to randomization, these assessments are to be repeated as clinically indicated. Eligibility criteria will be based on local laboratory values, which must be forwarded to the local laboratory management vendor. Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening.

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

- Informed consent information
- Failed inclusion/exclusion criteria
- Demographics
- Serious adverse events (SAEs)

5.2 Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 1:1 fashion (Section 3.4) to receive cabozantinib in combination with atezolizumab or second NHT. Subjects should receive their first dose of study drug treatment within 3 days after randomization.

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

The following are reminders for procedures and assessments during the treatment period:

- Cabozantinib and second NHTs are dosed once daily (prednisone is dosed twice daily).
- Doses of atezolizumab should be administered every 3 weeks and no more frequently than every 19 days (see Section 6.2.3.1). If atezolizumab administration is not delayed for AE management, it should be administered within 24 days of the prior atezolizumab dose. Atezolizumab dosing can be delayed for up to 12 weeks, after which the Sponsor should be contacted to discuss potential treatment continuation.
    - Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The

acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

- Specific laboratory tests must be performed at an RSV and evaluated within 72 hours prior to each administration of atezolizumab (see Section 5.6.5). These assessments are not required prior to the first dose if there has been no change in subject's clinical status since screening.
- Safety will be assessed on a schedule based on date of first dose as described in Section 5. RSVs must occur at least every 3 weeks (± 3 days), even if there is a study treatment dose delay. In the experimental arm, an RSV is required within 72 hours prior to each planned infusion of atezolizumab (vital signs must be assessed within 60 min prior to initiation of the infusion), even if fewer than 3 weeks have elapsed since the last RSV. Once atezolizumab is restarted after a treatment delay, RSVs are to occur at least every 3 weeks (± 3 days) thereafter.
- For subjects receiving abiraterone plus prednisone, serum ALT, AST, and total bilirubin assessments (liver function tests [LFTs]) are to be performed every 2 weeks for the first 12 weeks of treatment, in addition to at each RSV (Appendix B). If an LFT visit coincides with an RSV, duplicate LFTs do not need to be performed. After the first 12 weeks of treatment, LFTs will continue to be performed at each RSV.
- Unscheduled visits may occur at any time (Section 5.5).
- Radiographic tumor assessments are to be performed every 9 weeks (± 7 days) through Week 28 (ie, the first three on-study tumor assessments) and then every 12 weeks (± 7 days) relative to the date of randomization and irrespective of the dates of RSVs. For more details, see Section 5.6.6. PSA, HRQOL, and pain assessments after RSV1 are to occur with scheduled radiographic tumor assessments. For more details, see Sections 5.6.7, 5.6.8, and 5.6.9, respectively.
- PK, anti-drug antibodies (ADA), and biomarker sample collection schedules are per schedule of assessments (Appendix A and Appendix B).

The schedule of tumor assessments should be maintained regardless of whether study treatment is given, reduced, held or discontinued until a criterion for ending radiographic assessments is met (see Section 5.6.6.1).

In accordance with the ITT principle, radiographic tumor, PSA, HRQOL, and pain assessments, and survival follow-up, are to be performed per protocol even for subjects randomized who never receive study treatment.

Subjects may receive study treatment, even after protocol-defined progression, until they are no longer clinically benefitting in the opinion of the Investigator, unless they 1) need subsequent systemic anticancer treatment or urgent tumor-directed alternative medical intervention (eg, to CNS metastases), 2) experience unacceptable toxicity, or 3) have any other reason for treatment discontinuation as listed in the protocol (Section 3.5.1). In the absence of such, continued treatment after radiographic progression may occur in subjects who meet both of the following criteria:

- Clinical benefit per Investigator judgment
- ECOG performance status 0 or 1

Crossover among treatment arms will not be allowed.

Study completion is defined in Section 3.5.3

5.3 Post-Treatment Period

A first Post-Treatment Follow-up Visit (FU-1) for safety assessment is to occur at least 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision of the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by the subject). A second follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Refer to Appendix B for a description of all the assessments at this visit. Further details on follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix J.

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

In addition, subjects are to be contacted every 8 weeks (± 7 days) after FU-2 to assess survival status and document receipt of nonprotocol anticancer therapy (NPACT). This will continue until the subject expires or the Sponsor decides to discontinue collection of these data in the study. Every effort must be made to collect these protocol-specific evaluations unless consent to provide these data is withdrawn.

At each contact, the Investigator (or designee) will determine the subject's survival status and collect information on any systemic NPACT the subject has received. If the subject has died, the Investigator will record the date and cause of death as best can be determined. All efforts must be

undertaken by the study sites to determine the date of death (or date subject last known alive at the time of a data cutoff). This may include, but not necessarily be limited to, telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records. If a subject is lost to follow-up, multiple attempts to contact the study subject or designee must be documented in the subject records.

Unless new systemic anticancer therapy has been initiated, HRQOL, PSA, pain, and radiographic tumor assessments are to continue regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment as described in Section 5.6.6. Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

5.4 Maintenance Phase/Treatment after Study Completion

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (see Section 3.5.3). When sufficient data have been collected to adequately evaluate all study endpoints, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes to have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects on assigned study treatment will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.5.1). Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests, ECG, symptom-directed physical examination and vital signs) and tumor assessments every 12 weeks (or more frequently as clinically indicated) for as long as they are in this phase (Appendix C).

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs (Table 8-1), and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol (Section 8.2.3).

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

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

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

5.5 Unscheduled Visits or Assessments

If the Investigator determines that a subject should be monitored more frequently or with additional laboratory parameters assessments than indicated by the protocol-defined visit schedule, unscheduled visits or assessments are permitted. Local laboratory results obtained at unscheduled visits must be forwarded to the local laboratory management vendor. If multiple results are obtained within a short time frame (eg, within a given day or over the course of a few days), results representative of the subject's clinical course are to be submitted (every result need not be provided).

5.6 Procedure Details

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

5.6.1 Demographics, Baseline Characteristics, Medical and Cancer History

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

5.6.2 Physical Examination

Physical examinations will include height (screening visit only), weight, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examination will be conducted on RSV1 before first dose of study treatment and after randomization. Any ongoing/intercurrent condition

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

The ECOG performance status of the subject will be assessed during screening and at each scheduled safety assessment starting on RSV1 (Appendix D).

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

5.6.3 Vital Signs

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

Refer to Appendix B for the schedule of these assessments.

5.6.4 Electrocardiogram (ECG) Assessments

At screening and during the study, single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine the corrected QT interval calculated by the Fridericia formula (QTcF). If at any time a single ECG shows a QTcF with an absolute value > 480 ms at screening or > 500 ms at RSV1 onwards or an increase in QTcF of > 60 ms above baseline at RSV1 onwards, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used as the value assessed (see Section 6.6.1.1.16).

ECGs will be performed at the time points indicated in Appendix B. An ECG assessment is not required prior to the first dose if there has been no change in subject's clinical status since screening per Investigator judgment.

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

The Fridericia formula is depicted below for calculation of the 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)

5.6.5 Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for screening assessments is provided in Appendix A. The schedule for laboratory assessments is provided in Appendix B. Laboratory tests to establish eligibility must be done within 21 days before randomization unless otherwise stated. If there is a change in clinical status after screening and prior to randomization, these assessments are to be repeated as clinically indicated.

Hematology, serum chemistry, coagulation, UPCR including components, 24-hour urine protein, serum testosterone, PSA, hepatitis, and thyroid function tests are to be performed by a local laboratory. Results from these tests must be forwarded to the study local laboratory management vendor at screening and at any scheduled or unscheduled visit. If multiple results are obtained within a short time frame (eg, within a given day or over the course of a few days), results representative of the subject's clinical course are to be submitted (every result need not be provided).

Results or status from routine (dipstick) analysis and microscopic urine examination tests will be recorded on CRFs but will not be submitted to the study local laboratory management vendor.

Other specific laboratory test information:

- To confirm suitability for treatment, all laboratory tests must be performed within 21 days prior to administering the first dose of study treatment. Tests performed on RSV1 should be available to and deemed acceptable by the Investigator prior to any treatment being administered.
- Serum chemistry, hematology, coagulation, and urinalysis laboratory samples must be collected at an RSV within 72 hours and the results must be reviewed before any atezolizumab infusion administered on study. If the subject has symptoms indicative of a thyroid function disorder, thyroid function test results are to be reviewed prior to

administering atezolizumab. These assessments are not required prior to the first dose if there has been no change in subject's clinical status since screening.

- Direct and indirect bilirubin assessments are not required when the total bilirubin is normal or low.
- UPCR tests are to be performed at every RSV through RSV17, then at every 2 RSVs thereafter. UPCR tests are not required prior to the first dose if there has been no change in subject's clinical status since screening per Investigator judgment.
- For subjects receiving abiraterone plus prednisone, serum ALT, AST, and total bilirubin assessments (LFTs) are to be performed every 2 weeks for the first 12 weeks of treatment, in addition to at each RSV (Appendix B). If an LFT visit coincides with an RSV, duplicate LFTs do not need to be performed. After the first 12 weeks of treatment, LFTs will continue to be performed at each RSV.
- Serum testosterone will be assessed at screening only.
- C-reactive protein (CRP) test will be performed at screening only, if available at the local laboratory. For subjects already enrolled, CRP analyses may be performed on available screening samples.
- HIV test will be performed at screening if required by local regulation. Do not forward results from this test to the study local laboratory management vendor.

Table 5-1: Local Laboratory Panels

Hematology

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

Coagulation

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

Thyroid function

- thyroid-stimulating hormone (TSH)
- free thyroxine (T4)

Serum Chemistry

- albumin
- total alkaline phosphatase (ALP)
- amylase (if available)
- alanine amino transferase (ALT)
- aspartate amino transferase (AST)
- blood urea nitrogen (BUN) or urea
- C-reactive protein (CRP [screening only, if available])
- calcium
- bicarbonate (if available)
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin (conjugated and unconjugated fractions if total bilirubin is high)
- total protein

Urine Chemistry

- protein (spot urine; fully quantitative)
- creatinine (spot urine; fully quantitative)
- urine protein/creatinine ratio (UPCR; spot urine)
- 24-hour urine protein: perform at the discretion of the Investigator based on increases in UPCR from routine assessments

Virology

- hepatitis B surface antigen, (screening)
- hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive [screening])
- HIV test (if required by local regulation [screening])

Urinalysis
(Dipstick or Routine per Institutional Standard)

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

Microscopic Urine Examination

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

Other Laboratory Analyses

- testosterone (serum, screening only)
- prostate-specific antigen (PSA)

Table 5-2: Estimation of the Creatinine Clearance by Cockcroft and Gault

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

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

5.6.6 Tumor Assessments

5.6.6.1 General

Radiographic response and PD will be determined using RECIST 1.1 (Appendix H). For the purpose of determination of the multiple-primary endpoint, PFS, and of the secondary endpoint, ORR, central review of radiographic images will be conducted by a BIRC. The additional endpoint of PFS per PCWG3 will be determined by soft tissue progression based on CT/MRI per RECIST 1.1 or bone disease progression based on bone scan per PCWG3 and will be assessed by BIRC. All radiographic tumor assessments will be promptly sent to the BIRC until the primary analysis for the primary endpoint of PFS is completed. The BIRC will also review prior radiation history data for the purpose of selection of target lesions. Sites will be provided with instructions on how images should be collected and submitted to the BIRC. Radiographic assessments per RECIST 1.1 as per the Investigator may be used for treatment decisions; that is, study treatment(s) may be discontinued upon locally determined radiographic progression if the patient is no longer felt to be clinically benefitting. Study staff shall ensure that no images contain personal data as defined by applicable local, regional, and international laws and regulations.

Radiographic tumor assessments will include the following:

Chest / Abdomen / Pelvis (CAP): Computerized tomography (CT) of CAP or chest CT and abdomen/pelvis magnetic resonance imaging (MRI) will be performed in all subjects at

screening prior to randomization. Tumor assessments after randomization are to be performed every 9 weeks ± 7 days through Week 28 (ie, the first three on-study tumor assessments), and then every 12 weeks ± 7 days as per PCWG3 guidelines. Additional imaging of potential disease sites should be performed whenever radiographic disease progression (PD) is suspected.

Brain: MRI (or CT) of the brain will be performed only if clinically indicated at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis or if clinically indicated following the same post-baseline frequency as the imaging for CAP. MRI is the preferred method for brain scans. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless MRI is contraindicated. Note: For eligibility requirements regarding prior treatment of brain metastasis, refer to Section 4.3.

Bone: Technetium-99m bone scans (TBS) are to be performed at screening for all subjects. Evidence of or suspicion for soft tissue masses extending from bone must be corroborated with CT at screening. If a screening CT scan shows measurable soft tissue disease extending from bone, that soft tissue disease must be followed by on-study CT when CAP imaging (not capturing the lesion) is done. After randomization, TBS are to be performed on all subjects on the same schedule as for CAP. Subjects who report new symptoms associated with new or worsening bone scan lesions must have bone-directed CT performed (unless already captured by routine CT), which are to continue on the same schedule as for CAP.

Subjects who are treated beyond radiographic disease progression will continue to undergo tumor assessments at the frequency described above until study treatment is discontinued.

The same imaging modalities used at screening must be used for subsequent tumor assessments after randomization. If there is clinical concern regarding the administration of any contrast, then a non-contrast CAP imaging study is acceptable as a screening assessment if it clearly demonstrates soft tissue disease that can be followed without the need for contrast. If, at a follow up imaging time point, the use of contrast is prohibited (eg, due to acquired impaired renal function or contrast allergy) then the same modality should be used without contrast.

Tumor assessments should continue on the protocol-defined schedule, relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued. Guidance for continuation or termination of tumor assessments based on subject status is provided in Table 5-3.

Table 5-3: Criteria for Discontinuing Radiographic Assessments

Subject Status		
Study Treatment Discontinued?	**Investigator-Assessed rPD per RECIST 1.1 Reached?**	**Action with Radiographic Assessments**
No	No	Continue radiographic assessments
No	Yes	Continue radiographic assessments (ie, Investigator-assessed clinical benefit after radiographic progression)
Yes	No	Continue radiographic assessments unless receipt of new systemic therapy has been documented
Yes	Yes	Discontinue radiographic assessments

rPD, radiographic progressive disease; RECIST 1.1, Response Evaluation Criteria for Solid Tumors version 1.1.

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

Refer to Appendix B for the schedule for these assessments.

5.6.6.2 Confirmation of Tumor Response and Tumor Progression

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

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have tumor measurement outcomes confirmed by the Investigator after the initial Investigator-assessed PD criteria were met. This is to be performed no later than the next scheduled tumor assessment. Unless subjects 1) need subsequent systemic anticancer treatment or urgent tumor-directed alternative medical intervention (eg, to CNS metastases), 2) experience unacceptable toxicity, or 3) have any other reason for treatment discontinuation as listed in the protocol (Section 3.5.1), continuation of

study treatment after documentation of PD is allowed for those who meet both of the following criteria:

- Clinical benefit per Investigator judgment
- ECOG performance status of 0 or 1

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

For subjects who continue treatment after the documentation of radiographic PD, regularly scheduled imaging will continue until treatment discontinuation.

5.6.6.3 Blinded Independent Radiology Committee (BIRC)

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease must be sent to the BIRC preferably in original Digital Imaging and Communications in Medicine (DICOM) format (as detailed in the Site-specific Imaging Core Manual). The BIRC will evaluate prior radiation history for the purpose of valid identification of target lesions and all images in a central and independent fashion as further described in Section 12.2. Electronic transfer of scan files (via FTP, HTTP, or similar means) is preferred, although transfer on physical media (such as DVDs or CDs) is acceptable. For digital media, each disk should contain one time point for one subject. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, GCPs, and federal, international and/or state legal and medical requirements. The Sponsor and or designee will retain the media for the life of the study.

5.6.7 Prostate-Specific Antigen Assessments

Serum PSA levels will be assessed in all subjects at screening. Subsequent assessments will occur with scheduled imaging. PSA assessments should not be used to make study treatment decisions in this study. Refer to Appendix A and Appendix B for the schedule for these assessments.

5.6.8 Health-related Quality of Life Assessments

Health-related quality of life (HRQOL) assessments will be performed using the instruments EuroQol Health questionnaire EQ-5D-5L (Appendix K) and EORTC questionnaire QLQ-C30 (Appendix L). The EQ-5D-5L is a standardized instrument for use as a measure of self-reported general health status. It comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated

from EQ-5D-5L assessments are recommended for and commonly used in cost effectiveness analysis. The EORTC QLQ-C30 is a core questionnaire that is validated for assessment of quality of life of cancer patients. It consists of functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, and nausea and vomiting), global health status and quality of life scale, and several single-item symptom measures.

The first HRQOL assessment will be prior to first dose of study treatment on RSV1, and subsequent assessments will occur with scheduled imaging. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects (Appendix B).

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

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

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

Translated copies of the EQ-5D-5L and EORTC QLQ-C30 questionnaires, if required, and instructions for filling them out will be provided to each study site in a separate study manual. HRQOL assessments will no longer be collected if the study transitions to the Maintenance Phase.

5.6.9 Pain Assessments

Assessment of pain will be self-reported by each subject using an 11-point (from 0 to 10) NRS measuring worst pain in the last week, with 0 representing “No Pain” and 10 representing “Pain as Bad as You Can Imagine” (Appendix M). The 11-point NRS measuring worst pain severity is a validated and commonly used assessment across diseases and treatment (Dworkin et al 2005).

Baseline pain assessments will be performed prior to first dose of study treatment on RSV1, and subsequent pain assessments will be performed with scheduled imaging.

In addition, new or increased use of analgesics from baseline will continuously be assessed by the Investigator. A new analgesic is defined as one that is taken for at least seven consecutive days after, but not prior to, randomization. Increased use is defined as an increased dose of an analgesic taken after randomization relative to baseline (ie, dose taken at screening) for analgesics taken for at least seven consecutive days.

Subjects will continue reporting pain scores and analgesic use regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects (Appendix B).

Subjects are to complete the pain assessments at the start of each clinic visit. Ideally, study subjects should not receive any information about their most recent medical results prior to completing the pain assessment to minimize bias. Subjects are to independently respond to pain questionnaires on their own.

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

Translated copies of the pain questionnaire, if required, and instructions for filling them out will be provided to each study site in a separate study worksheet. Pain assessments will no longer be collected if the study transitions to the Maintenance Phase.

5.6.10 Symptomatic Skeletal Events

Symptomatic skeletal events will be continuously assessed from RSV1 through the FU-2 visit. The definition of an SSE is an instance of any one of the following: radiation therapy to bone, surgery to bone, spinal cord compression, or symptomatic fracture.

5.6.11 Health Care Resource Utilization

Health care resource utilization parameters will be collected from randomization through the FU-2 visit. These include hospital admissions, emergency room visits, intensive care unit

admissions, length of stay, surgeries, and transfusions. These data will not be collected in the Maintenance Phase.

5.6.12 Pharmacokinetic Assessments

Blood samples for PK assessment will be obtained from all subjects in the cabozantinib plus atezolizumab combination arm. Samples will be collected for plasma cabozantinib concentration measurement predose on RSV1, RSV2, RSV3, RSV4, and RSV5. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib taken in combination with atezolizumab in this population.

Serum concentrations of atezolizumab will be measured in the cabozantinib plus atezolizumab combination arm. Samples will be collected for serum atezolizumab concentration measurement predose on RSV1, RSV3, RSV5, and RSV9, RSV16, RSV19, and FU-1 and FU-2 visits. The results will be used to confirm exposure to atezolizumab.

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

5.6.13 Immunogenicity Assessments

Blood samples will be obtained from all subjects in the cabozantinib plus atezolizumab combination arm for immunogenicity assessment (anti-drug antibodies [ADA]) predose on RSV1, RSV3, RSV5, RSV9, RSV16, RSV19, and FU-1 and FU-2 visits. Samples may be analyzed for neutralizing ADA response to atezolizumab if ADA testing is positive, as applicable.

5.6.14 Biomarker Assessments

The schedule of biomarker assessments is specified in Appendix A and Appendix B. The samples include:

- Tumor samples (archival or fresh tumor biopsy; recommended but not required)
    - If archival tumor tissue is not available, a fresh tumor biopsy may be obtained prior to first dose of study treatment
    - A fresh tumor tissue biopsy may also be performed at disease progression.
- Peripheral blood

Please refer to Section 6.6.1.1.7 for guidance regarding biopsies.

Exploratory analyses may include but are not limited to the following:

- Targets of the study drugs (eg, PD-L1, MET) and relevant biomarker expression levels
- Tumor characteristics (eg, immune cell infiltration, tumor mutational burden [TMB]) in tumor specimens
- Plasma biomarkers (eg, cytokines/chemokines)
- Circulating tumor cells (CTCs)
- Circulating tumor (ctDNA)

A pharmacogenetic blood sample will be collected pre-dose on the first day of treatment (RSV1) and may be used for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with the pharmacokinetics, safety, tolerability, and/or response to the study drug combination. This sample may also be used for assay development to facilitate identification of novel predictive biomarker profiles and improve treatment strategies.

Collection of biomarker samples may be halted early or sampling frequency may be modified at the discretion of the Sponsor. These samples will no longer be collected if the study transitions to the Maintenance Phase.

5.6.15 Overall Survival

Overall survival will be assessed every 8 weeks (± 7 days) after the FU-2 visit, which occurs 100 days (±14 days) after discontinuation of study treatment. Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data. Receipt of subsequent NPACT will also be collected during follow-up contacts. If a subject withdraws consent to participate in the study, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations.

5.7 Protocol Deviations

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

6 TREATMENTS

6.1 Composition, Formulation, and Storage

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

6.1.1 Study Treatment

6.1.1.1 Cabozantinib Tablets

The Sponsor will provide each investigator adequate supplies of cabozantinib, which will be supplied as 20-mg yellow film-coated round tablets. The components of the tablets are listed in Table 6-1.

Table 6-1: Cabozantinib Tablet Components and Composition

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

HPMC, Hydroxypropyl methylcellulose
[a] weight fraction, expressed in percentage

Refer to the Pharmacy Manual for details on storage and handling of cabozantinib.

6.1.1.2 Atezolizumab

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

The Sponsor will provide each investigator with adequate supplies of atezolizumab, which will be supplied as a 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in single-dose vials. Atezolizumab solution contains the following inactive ingredients: glacial acetic acid,

L-histidine, sucrose, and polysorbate 20. Refer to the package insert (or the local label) and the pharmacy manual for additional information and instructions for preparing atezolizumab for infusion. Commercially sourced solution used as diluent (0.9% NaCl) should be obtained by investigative sites according to local regulations.

6.1.1.3 Novel Hormonal Therapy (Abiraterone with Prednisone, or Enzalutamide)

Subjects in the control arm will receive the Investigator's choice (as selected prior to randomization) of one of the following:

- Abiraterone (1000 mg po qd) plus prednisone (5 mg po bid)
- Enzalutamide (160 mg po qd)

Refer to the most current local prescribing information appropriate to the respective site location for detailed information on abiraterone, prednisone, and enzalutamide. All drugs will be provided centrally by the Sponsor or locally by the site, subsidiary or designee, depending on the local operational and/or regulatory requirements.

6.2 Treatment Schedule of Administration

6.2.1 Experimental Arm: Cabozantinib in Combination with Atezolizumab

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

Subjects will receive study treatment with cabozantinib and atezolizumab as long as they continue to experience clinical benefit as assessed by the Investigator (Section 5.6.6.2) or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5.1). Subjects may be allowed to discontinue one component of the study treatment but continue to receive the other; Investigators are encouraged to consult with the Sponsor before doing so.

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

6.2.2 Control Arm: NHT (Abiraterone with Prednisone, or Enzalutamide)

The recommended dose for abiraterone is 1000 mg po qd. Abiraterone is to be taken with prednisone (5 mg po bid). Dose reduction of abiraterone to 500 mg qd is permitted for hepatotoxicity.

The recommended dose for enzalutamide is 160 mg po qd. Dose reduction of enzalutamide to 120 mg qd or 80 mg qd is permitted for toxicity.

Subjects will receive study treatment with either 1) abiraterone with prednisone, or 2) enzalutamide as long as they continue to experience clinical benefit as assessed by the Investigator (Section 5.6.6.2) or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.5.1). Subjects randomized to the control arm may not switch from their pre-assigned NHT to the other NHT while on study.

For detailed guidance on the administration of abiraterone plus prednisone, and enzalutamide, refer to the most current prescribing information appropriate to the respective site location.

6.2.3 Study Drug Administration in the Clinic

The first dose of study treatment is to occur within 3 days after randomization. RSV1 is to occur no more than 72 hours prior to the first dose of study treatment. The first doses of all study treatments are to be administered at the clinic.

6.2.3.1 Experimental Arm: Cabozantinib plus Atezolizumab

Atezolizumab

For subjects on the experimental arm (cabozantinib in combination with atezolizumab), atezolizumab is to be administered first.

Atezolizumab should be administered every 3 weeks and no more frequently than every 19 days. If atezolizumab administration is not delayed for AE management, it should be administered within 24 days of the prior atezolizumab dose. Doses of atezolizumab are scheduled to be administered intravenously at the clinic by infusion on Day 1 of each 21-day cycles (-2 days/+3 days). Cycles may be longer than 3 weeks if atezolizumab treatment is delayed due to toxicity or other reasons.

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

indicated, vital signs should be measured every 15 (± 5) minutes during subsequent infusions and at 30 (± 10) minutes after each subsequent infusion. Premedication for IRRs or CRS is allowed after the initial infusion. No bolus or IV push of atezolizumab is allowed. Dose delays will be allowed for toxicities suspected to be due to atezolizumab administration. Atezolizumab infusion requirements and guidance are summarized in Table 6-2.

Table 6-2: Atezolizumab Infusion Requirements and Guidance

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

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

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

Cabozantinib

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

For cabozantinib dosing on subsequent dosing days refer to Section 6.2.4.

6.2.3.2 Control Arm: Abiraterone plus Prednisone, or Enzalutamide

Abiraterone plus Prednisone

On the first dosing day subjects are to take abiraterone on an empty stomach, either one hour before or two hours after a meal, while under observation at the clinic to monitor for potential AEs. The tablets are to be swallowed whole with water and should not be crushed or chewed.

The first oral dose of prednisone will be taken with abiraterone while under observation in the clinic to monitor for potential AEs. The second oral dose of prednisone may be taken outside the clinic. Prednisone is to be taken with food and should be swallowed whole and not broken, divided, or chewed.

Subsequent doses of abiraterone and prednisone will be self-administered outside the clinic (Section 6.2.5).

Enzalutamide

On the first dosing day subjects will take enzalutamide, with or without food, while under observation at the clinic to monitor for potential AEs. The capsules are to be swallowed whole and not to be chewed, dissolved, or opened.

Subsequent doses of enzalutamide will be self-administered outside the clinic (Section 6.2.5).

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

6.2.4 Experimental Arm: Cabozantinib Administration Outside the Clinic

Subjects in the experimental arm (cabozantinib + atezolizumab) should take cabozantinib outside the clinic at approximately the same time every day, preferentially before going to bed, and should adhere to the fasting requirements described in this section.

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

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

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

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

6.2.5 Control Arm: Abiraterone with Prednisone, or Enzalutamide Administration outside the Clinic

Abiraterone plus Prednisone

Abiraterone should be taken orally once daily. Abiraterone should be taken on an empty stomach, either one hour before or two hours after a meal. The tablets are to be swallowed whole with water and not crushed or chewed. Subjects should be instructed that if a dose of abiraterone is missed, the prescribed dose should be taken the following day. Subjects should not take more than the prescribed doses of abiraterone or prednisone each day.

Prednisone is to be taken with abiraterone. Prednisone is to be taken orally twice daily with food and should be swallowed whole and not broken, divided, or chewed. For missed doses, subjects should be told to take the missed dose as soon as they remember. If it is almost time for the next dose, the missed dose should be skipped and the medicine taken at the next regularly schedule time. Subjects should not take an extra dose to make up for the missed dose. Subjects should be warned not to discontinue the use of prednisone abruptly or without medical supervision.

Enzalutamide

Enzalutamide should be taken orally once daily, at the same time each day. Enzalutamide can be taken with or without food. The capsules are to be swallowed whole and not to be chewed, dissolved, or opened. Subjects should be instructed that if a dose of enzalutamide is missed, the prescribed dose should be taken as soon as remembered on that day. If the daily dose is missed, then the prescribed dose should be taken at the regular time the next day. Subjects should not take more than the prescribed dose of enzalutamide each day.

Refer to the most current abiraterone, prednisone, and enzalutamide prescribing information appropriate to the respective site location for more details regarding recent major label changes,

indication and usage, dosage and administration, dose modifications, contraindications, warnings and precautions, adverse reactions, drug interactions, and use in specific populations.

6.3 Treatment after Study Completion

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

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

a) The study is terminated due to safety concerns.

b) The development of atezolizumab or cabozantinib is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives (eg, the null hypothesis is rejected for neither PFS nor OS).

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

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

6.4 Compliance

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

6.5 Study Treatment Accountability

The Investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Drug accountability will be

performed periodically by the Sponsor or designee at interim monitoring visits. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

6.6 Safety Considerations

Subjects will be monitored for SAEs from the time of signing informed consent and for nonserious AEs from first dose of study treatment. Monitoring for nonserious AEs continues through the FU-1 visit (FU-2 visit for AESIs [Table 8-1] regardless of seriousness and for unrelated SAEs). Longer monitoring periods are required for related SAEs and certain other events as described in Section 8.4. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix J. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should, at a minimum, take into account confounding factors such as underlying disease and concomitant medications. Adverse event severity will be graded by the Investigator according to CTCAE v5.

For the combination study treatment (experimental arm), the following should be taken into consideration in decisions regarding management for treatment-related side effects:

- Cabozantinib and atezolizumab have class-specific safety profiles based on their mechanisms of action but may also cause AEs that overlap. For management of AEs clearly attributed to cabozantinib or atezolizumab, independent dose modification for either agent is allowed.
    - Examples of VEGFR-TKI associated AEs caused by cabozantinib are hypertension and hand-foot syndrome.
    - Examples of AESIs caused by atezolizumab are pneumonitis and endocrinopathies.
- For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications of both agents per the discretion of the Investigator.
    - Examples of overlapping AEs are diarrhea and transaminase increases.

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

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

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

Although most irAEs observed with immunomodulatory agents have been mild and limiting, in severe cases immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. Given that the discontinuation of atezolizumab alone may not lead to rapid alleviation of symptoms and may not be sufficient for management of some irAEs, such events should be recognized early and treated promptly to avoid potential major complications. For detailed guidance on the management of irAEs associated with atezolizumab, see Section 6.6.2.1.

Dose interruptions and/or reductions of cabozantinib or delays of atezolizumab (atezolizumab reductions are not allowed) for AEs may occur at any time and independently at the discretion of the Investigator. If either or both study treatments are interrupted for more than 12 weeks, the Sponsor should be contacted to discuss potential treatment continuation. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

For recommendations on dose modifications of cabozantinib treatment, see Section 6.6.1; for recommendations on dose modifications of atezolizumab treatment, see Section 6.6.2.

Dose interruptions or reductions of abiraterone or of enzalutamide for AEs may also occur at any time at the discretion of the Investigator. If study treatment is interrupted for more than 12 weeks, the Sponsor should be contacted to discuss potential treatment continuation. Refer to the most current abiraterone, prednisone, or enzalutamide prescribing information appropriate to the respective site location for details regarding dose interruptions and dose modifications.

6.6.1 Management of AEs Associated with Cabozantinib

The assigned dose for cabozantinib in the experimental arm is 40 mg qd. Considerations for management of AEs associated with cabozantinib are presented below.

- Two dose reduction levels of cabozantinib (20 mg daily, and 20 mg every other day [qod]) are permitted on the experimental arm (see Table 6-3).

- Dose modification criteria for treatment-related AEs of cabozantinib are shown in Table 6-4.

- Guidance for dose reinstitution and reescalation after dose interruptions and/or reductions are as follows:

    - If the subject recovers from his toxicities to ≤ Grade 1 per CTCAE v5 or to the baseline value (or lower) and the AE was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.

    - If the subject recovers from his toxicities to ≤ Grade 1 or to the baseline value (or lower) and the AE was deemed possibly related to cabozantinib, then cabozantinib may be restarted at the same dose or at a reduced dose (see Table 6-4), as deemed appropriate by the Investigator. Furthermore, subjects who initiated treatment with cabozantinib at 40 mg and experience a possibly related AE of Grade 1 or 2 severity may be restarted with no dose change after recovery of the toxicities to ≤ Grade 1 or to the baseline value (or lower) if appropriate supportive care can prevent or minimize the risk of the AE.

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

    - Reescalation to the previous dose may be allowed at the discretion of the Investigator but no sooner than 2 weeks beyond recovery to Grade 1 (or baseline grade) with the event deemed tolerable and easily managed by optimized supportive treatment.

    - Dose reescalation is not allowed following a cabozantinib-related dose reduction for Grade 4 hematological toxicities or Grade 4 AEs affecting major organs (eg, CNS, cardiac, hepatic, renal, pulmonary, GI).

- Guidelines for the management of specific AEs of cabozantinib such as GI disorders, non-GI fistula formation, hemorrhage, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, hepatocellular toxicity, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders are provided in Section 6.6.1.1.

Table 6-3: Dose Levels of Cabozantinib (Oral Dosing)

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

[a] Cabozantinib will be discontinued in the experimental arm if a dose of 20-mg cabozantinib every other day is not tolerated.

Table 6-4: General Dose Modification Guidelines for Cabozantinib-Related AEs

CTCAE v5 Grade	Recommended Guidelines for Management
Grade 1 or 2 AEs that are tolerable and are easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable.
Grade 1 or 2 AEs that are **intolerable and cannot be adequately managed** Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction of cabozantinib and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib must be interrupted immediately. In general, cabozantinib should be discontinued unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction of cabozantinib following recovery to Grade 1 (or baseline) and optimal medical care Sponsor must be contacted to discuss treatment continuation upon resolution of AEs.

AE, adverse event.
Note: Cabozantinib dose modification criteria for specific medical conditions are provided in Section 6.6.1.1.

6.6.1.1 Warnings, Precautions, and Management Guidelines for Adverse Events Associated with Cabozantinib Treatment

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

Other medically important but less frequent AEs include arterial thrombotic AEs (eg, TIA, and MI) and venous thrombotic AEs (eg, DVT and PE), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; preferred term: posterior reversible encephalopathy syndrome [PRES]).

Adverse events associated with laboratory test abnormalities that were experienced by ≥ 5% of cabozantinib-treated subjects 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, alkaline phosphatase (ALP) increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPE, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 6-3).

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

6.6.1.1.1 Gastrointestinal Disorders

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

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 6-5. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per Investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

Table 6-5: Management of Diarrhea Associated with Cabozantinib

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

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

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 7.3 for further details).

6.6.1.1.2 Non-Gastrointestinal Fistula

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

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

6.6.1.1.3 Hemorrhage

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

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

6.6.1.1.4 Thromboembolic events

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

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

6.6.1.1.5 Hypertension

Table 6-6 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a

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

Cabozantinib should be discontinued in subjects with hypertension with life threatening consequences or when urgent intervention is indicated, and appropriate medical management should be initiated.

Table 6-6: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP ≤ 150 mm Hg systolic and ≤ 90 mm Hg diastolic • If subject is symptomatic, interrupt cabozantinib treatment and restart only if symptoms have resolved and BP is ≤ 150 mm Hg systolic and ≤ 90 mm Hg diastolic
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per Investigator discretion. Treatment should be interrupted if upper limits of systolic BP (≥ 160 mm Hg) or diastolic BP (≥ 110 mm Hg) are sustained and not adequately manageable, or if systolic BP is > 180 mm Hg, or if subject is symptomatic. • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP ≤ 150 mm Hg systolic and ≤ 90 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Re-start cabozantinib treatment at reduced dose and re-escalate only if BP falls to and is sustained at ≤ 150 mm Hg systolic and ≤ 90 mm Hg diastolic
Hypertension with life threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	• Discontinue cabozantinib treatment • Initiate appropriate medical management

BP, blood pressure.

[a] The Investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP > 150 mm Hg or diastolic BP > 90 mm Hg based on their clinical judgment and assessment of the individual subject.

6.6.1.1.6 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 (eg, with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

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

6.6.1.1.7 Skin and Subcutaneous Tissue Disorders

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

Treatment with cabozantinib should be stopped at least 28 days prior to elective surgery (for tumor biopsies at least 10 days before the procedure). The decision to resume treatment with cabozantinib after surgery or biopsies should be based on clinical judgment of adequate wound healing.

For biopsies collected via major surgery, please consult with the Sponsor.

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

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

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPE are summarized in Table 6-7.

Table 6-7: Management of Palmar-plantar Erythrodysesthesia (PPE) Associated with Cabozantinib

CTCAEv5 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume cabozantinib at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue subject from study treatment if PPE does not improve within 6 weeks.

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

6.6.1.1.8 Osteonecrosis

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

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

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

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

6.6.1.1.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR or 24-hour urine protein assessment. Table 6-8 provides treatment guidelines for proteinuria deemed related to cabozantinib.

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

Table 6-8: Management of Proteinuria Associated with Cabozantinib

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

UPCR, urine protein/creatinine ratio.

6.6.1.1.10 Nervous System Disorders

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

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

6.6.1.1.11 Hepatocellular Toxicity

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

Management guidelines for hepatotoxicity (hypertransaminasemia) related to cabozantinib treatment are provided in Table 6-9.

Table 6-9: Management of Hepatotoxicity Associated with Cabozantinib

Severity of Transaminase (ALT or AST) Elevation by 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 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 lab abnormalities have resolved to CTCAE Grade ≤ 1 or baseline grade. • Discontinue if lab abnormalities cannot be reversed despite interruption of cabozantinib or if Grade 3 or higher abnormality recurs upon rechallenge.
ALT or AST > 8 × ULN OR ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with DILI	• Discontinue cabozantinib

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DILI, drug-induced liver injury

6.6.1.1.12 Infections and Infestations

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

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

6.6.1.1.13 Blood and Lymphatic System Disorders

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

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

6.6.1.1.14 Fatigue

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

6.6.1.1.15 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.

6.6.1.1.16 Corrected QT Prolongation

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

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

If at any time on study there is an increase in QTcF to an absolute value > 480 ms at screening or > 500 ms at RSV1 onwards or an increase in QTcF of > 60 ms above baseline at RSV1 onwards, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or there is an increase of > 60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Send ECGs to central ECG reader for independent read
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms and the average increase is ≤ 60 ms above baseline, or a consulting cardiologist or appropriate expert determines that the frequency of ECGs may revert to the schedule in the protocol.

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

- Symptoms are determined to be unrelated to the QT interval prolongation
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms and ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

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

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

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

6.6.1.1.17 Electrolyte Disorders

Serum electrolyte imbalance including hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia have been reported during treatment with cabozantinib. There are many causes for an electrolyte imbalance including loss of body fluids (eg, from prolonged vomiting or diarrhea), inadequate diet, kidney disease and use of certain concomitant medications (eg, diuretics). Electrolyte imbalance may create a variety of symptoms. Examples include 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 as outlined in Table 6-4 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or IV replacement.

6.6.1.1.18 Endocrine Disorders

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

6.6.2 Management of AEs Associated with Atezolizumab

The assigned dose for atezolizumab is 1200 mg IV every 3 weeks. Infusion will occur every three weeks (-2 days).

- Dose interruptions are allowed for atezolizumab (see Table 6-10), but dose reductions are not allowed.
- Dose modification criteria for irAEs and for guidance on reinstituting atezolizumab are shown in Table 6-11.
- If corticosteroids are initiated for treatment of irAEs, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Guidelines for the management of IRRs and CRS, irAEs for atezolizumab (ie, pneumonitis, hepatitis, diarrhea/colitis, myocarditis, endocrinopathies including hypophysitis, and infection) and other AESIs are provided in Section 6.6.2.1.

Table 6-10: Dose Interruptions of Atezolizumab

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

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

Table 6-11: Guidance Overview for Atezolizumab Treatment Modifications

CTCAE v5 Grade	Recommended Management
Grade 1* or 2 pneumonitis Grade 1** pericarditis Grade 1 immune-mediated myelitis*** Grade 1 or 2 facial paresis**** Grade 2 nephritis Grade 2 hepatic events Grade 2 or 3 diarrhea or colitis Grade 2 or 3 myositis Symptomatic adrenal insufficiency; Grade 2 or 3 hypophysitis; or Grade 3 or 4 hyperglycemia, hypothyroidism, or hyperthyroidism Grade 2 ocular inflammatory toxicity Grade 2 or 3 pancreatitis or increases in amylase and/or lipase levels to > 2.0 - 5.0 × ULN, regardless of signs or symptoms, or to > 5.0 × ULN Grade 3 or 4 infection Grade 2 infusion-related reactions or cytokine-release syndrome Grade 3 rash Suspected Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade) Other Grade 2 or 3 atezolizumab-associated AEs	*Note: The guidance below applies to all events listed on the left column* Delay treatment with atezolizumab Treatment may be resumed in subjects following recovery to Grade 0-1. * For Grade 1 pneumonitis, consider withholding atezolizumab. ** For Grade 1 pericarditis, withhold treatment with atezolizumab and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly ***Continue atezolizumab unless symptoms worsen or do not improve ****If event resolves fully, resume atezolizumab

CTCAE v5 Grade	Recommended Management
Grade 2 - 4 myocarditis Grade 2 - 4 immune-mediated pericardial disorders Grade 2 - 4 immune-mediated myelitis Grade 4 myositis and/or recurrent Grade 3 myositis Grade 3 or 4 pneumonitis Grade 3 or 4 nephritis Grade 3 or 4 hepatic events Grade 3 or 4 immune-mediated neuropathy, including facial paresis Grade 4 diarrhea or colitis Grade 4 hypophysitis and/or recurrent hypophysitis Life-threatening immune-mediated hypothyroidism or hyperthyroidism Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades) Grade 3 or 4 ocular inflammatory toxicity Grade 4 or recurrent Grade 2 or 3 pancreatitis Grade 3 or 4 infusion-related reactions or cytokine-release syndrome Grade 4 rash Confirmed Stevens Johnson syndrome or toxic epidermal necrolysis (any grade) Other Grade 4 or recurrent Grade 3 atezolizumab-associated AEs	*Note: The guidance below applies to all events listed on the left column.* Permanently discontinue atezolizumab

AE, adverse event; ULN, upper limit of normal.

Note: Additional information for atezolizumab dose modification criteria and treatment recommendations for irAEs and infusion reactions are provided in Section 6.6.2.1.

6.6.2.1 Warnings, Precautions, and Management Guidelines for Adverse Events Associated with Atezolizumab Treatment

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

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible

IRAEs prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

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

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

Subjects treated with atezolizumab may also develop IRRs or CRS as well as irAEs such as myocarditis, pericardial disorders, pneumonitis, hepatitis, colitis, nephritis, endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, Type 1 diabetes), skin disorders and severe cutaneous adverse reactions, ocular events, neurological toxicity (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, meningoencephalitis, myelitis, or facial paresis), pancreatitis, myositis, and embryo-fetal toxicity. Management guidance for atezolizumab-associated AEs is provided in Sections 6.6.2.1.1 through 6.6.2.1.16.

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

6.6.2.1.1 Infusion-Related Reaction and Cytokine-Release Syndrome

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines

and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

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

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix G.

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

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

6.6.2.1.2 Immune-Related Pulmonary Events

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infections, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 6-12.

Table 6-12: Management Guidelines for Immune-Related Pulmonary Events, Including Pneumonitis

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

BAL, bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

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

6.6.2.1.3 Immune-Related Colitis or Diarrhea

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 6-13.

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

Table 6-13: Management Guidelines for Immune-Related Diarrhea or Colitis

Severity of Event	Management
Grade 1	• Continue atezolizumab • Initiate symptomatic treatment • Endoscopy is recommended if symptoms persist for > 7 days • Monitor closely
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Initiate symptomatic treatment • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Subject referral to GI specialist is recommended • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c]
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer subject to GI specialist for evaluation and confirmatory biopsy • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c]
Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor[c] • Refer subject to GI specialist for evaluation and confirmatory biopsy • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

GI, gastrointestinal; IV, intravenous

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.4 Immune-related Endocrinopathies

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 6-14.

Monitor for signs and symptoms of hypophysitis. Subjects with unexplained symptoms such as headache, fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The subject should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (eg, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test), and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 6-14: Management Guidelines for Endocrine Events

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

Event	Management
Hypothyroidism Grade 1	• Continue atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH closely
Hypothyroidism Grade 2	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hypothyroidism Grade 3 and 4	• Withhold atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH closely • Refer to endocrinologist • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Permanently discontinue atezolizumab and contact the Sponsor for life-threatening immune-mediated hypothyroidism.[b]
Hyperthyroidism Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L**: • Continue atezolizumab • Monitor TSH every 4 weeks • Consider subject referral to endocrinologist **TSH < 0.1 mU/L**: • Follow guidelines for Grade 2 hyperthyroidism • Consider subject referral to endocrinologist
Hyperthyroidism Grade 2	• Consider withholding atezolizumab • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider subject referral to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving
Hyperthyroidism Grade 3 and 4	• Withhold atezolizumab • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed • Refer to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Permanently discontinue atezolizumab and contact the Sponsor for life-threatening immune-mediated hyperthyroidism[b]

Event	Management
Symptomatic adrenal insufficiency Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset[a] • Refer subject to endocrinologist • Perform appropriate imaging • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • Resume atezolizumab if event resolves to Grade 1 or better and subject is stable on replacement therapy [c] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better or subject is not stable on replacement therapy while withholding atezolizumab[b]
Hyperglycemia Grade 1 or 2	• Continue atezolizumab • Investigate for diabetes. If subject has Type 1 diabetes, treat as a Grade 3 event. If subject does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control
Hyperglycemia Grade 3 or 4	• Withhold atezolizumab • Initiate treatment with insulin • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines • Monitor for glucose control • Resume atezolizumab when symptoms resolve and glucose levels are stable

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

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.5 Immune-Related Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 6-15.

Table 6-15: Atezolizumab Management Guidance of Immune-Related Dermatologic Events

Severity of Event	Management of Skin Disorder
Grade 1	• Continue atezolizumab • Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines)
Grade 2	• Continue atezolizumab • Consider subject referral to dermatologist for evaluation and, if indicated, biopsy • Initiate treatment with topical corticosteroids • Consider treatment with higher-potency topical corticosteroids if event does not improve • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day
Grade 3	• Delay atezolizumab for up to 12 weeks after event onset[a] • Refer subject to dermatologist for evaluation and, if indicated, biopsy • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1− 2 mg/kg/day if event does not improve within 48− 72 hours • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact Sponsor if event does not resolve to Grade 1 or better while whitholding atezolizumab[c]
Grade 4	• Permanently discontinue atezolizumab and contact Sponsor[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 subject to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy • Follow the applicable treatment and management guidelines above • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.6 Immune-Related Ocular Events

Treatment-emergent ocular events have been associated with atezolizumab. An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events). Management guidelines for ocular events are provided in Table 6-16.

Table 6-16: Atezolizumab Management Guidance of Immune-Related Ocular Events

Severity of Event	Management of Ocular Event
Grade 1	• Continue atezolizumab • Subject referral to ophthalmologist is strongly recommended • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy • If symptoms persist, treat as a Grade 2 event
Grade 2	• Delay atezolizumab for up to 12 weeks after event onset[a] • Subject referral to ophthalmologist is strongly recommended • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor[c] • Refer subject to ophthalmologist • Initiate treatment with 1− 2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.7 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, 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 subjects being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Subjects with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6-17.

Table 6-17: Management Guidelines for Immune-Related Meningoencephalitis

Severity of Event	Management
All grades	• Permanently discontinue atezolizumab and contact the Sponsor • Refer subject to neurologist • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

IV, intravenous.

6.6.2.1.8 Immune-Related Motor and Sensory Neuropathy

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 6-18, with specific guidelines for myelitis provided in Table 6-19.

Table 6-18: Management Guidelines for Immune-Related Neurologic Disorders

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

IV, intravenous.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

Table 6-19: Management Guidelines for Immune-Mediated Myelitis

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

6.6.2.1.9 Immune-Related Pancreatitis

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase (if available) and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 6-20.

Table 6-20: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase > ULN - 1.5 × ULN, Grade 1	• Continue atezolizumab • Monitor amylase (if available) and lipase prior to dosing
Amylase and/or lipase > 1.5 - 2.0 × ULN, or > 2.0 - 5.0 × ULN and asymptomatic, Grade 2	**Amylase and/or lipase > 1.5 - 2.0 × ULN:** • Continue atezolizumab • Monitor amylase (if available) and lipase weekly • For prolonged elevation (eg, > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent **Asymptomatic with amylase and/or lipase > 2.0 - 5.0 × ULN:** • Treat as Grade 3 amylase and/or lipase elevation
Amylase and/or lipase > 2.0 - 5.0 × ULN with signs or symptoms, or > 5.0 × ULN, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset[a] • Refer subject to GI specialist • Monitor amylase (if available) and lipase every other day • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c] • For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c]
Immune-related pancreatitis, Grade 2[d] or 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] • Refer subject to GI specialist • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • Resume atezolizumab if event resolves to Grade 1 or better[b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c] • For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c]

Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor[c] • Refer subject to GI specialist • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; IV, intravenous; ULN, upper limit of normal.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

[d] Per CTCAE v5, Grade 2 pancreatitis requires radiological findings in addition to enzyme elevation.

6.6.2.1.10 Immune-Mediated Cardiac Events

Immune-Related Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any subject presenting with signs or symptoms suggestive of myocarditis including, but not limited to, laboratory (eg, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral; eg, in a subject who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All subjects 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.

Subjects with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6-21.

Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis. Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability. Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly. All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated. Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6-21. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6-21: Management Guidelines for Immune-Related Cardiac Events

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

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

6.6.2.1.11 Immune-Related Nephritis

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible subjects must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Subjects 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 subject to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Subjects with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6-22.

Table 6-22: Management Guidelines for Immune-Related Nephritis

Event	Management
Renal event, Grade 1	• Continue atezolizumab • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer subject 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 the Sponsor [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor • Refer subject to renal specialist and consider renal biopsy • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.12 Immune-Related Myositis

Immune-related 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 creatinine-kinase increase), and imaging (electromyography/MRI) features and is confirmed with a muscle biopsy.

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

Subjects with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6-23.

Table 6-23: Management Guidelines for Immune-Related Myositis

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

Event	Management
Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor[c] • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

IV, intravenous

[a] Atezolizumab may be withheld for a period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

6.6.2.1.13 Immune-Related Hepatic Events

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible subjects 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 6-24.

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

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

Table 6-24: Management Guidelines for Hepatic Events

Severity of 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 • Resume atezolizumab if event resolves to Grade 1 or better [b] • Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better while withholding atezolizumab[c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor[c] • Consider subject referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury • Immediately initiate treatment with 1–2 mg/kg/day 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

GI, gastrointestinal; LFT, liver function test.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks after event onset to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.

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

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

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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, either of the following conditions requires permanent discontinuation of all study drugs, including atezolizumab, and reporting of the occurrence as a serious adverse event:

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN

- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

6.6.2.1.14 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

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

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

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

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

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

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

Subjects with suspected HLH or MAS should be treated according to the guidelines in Table 6-25.

Table 6-25: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

6.6.2.1.15 Other Atezolizumab-Associated Immune-Related Adverse Events

For management of other irAEs not included in Sections 6.6.2.1.1 through 6.6.2.1.14, the following general management guidance should be applied:

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

6.6.2.1.16 Embryo-Fetal Toxicity

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

6.6.3 Warnings, Precautions, and Management Guidelines for Adverse Events Associated with Abiraterone Plus Prednisone

Abiraterone

The most common adverse reactions (≥ 10%) associated with abiraterone are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache.

The most common laboratory abnormalities (> 20%) associated with abiraterone are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia.

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Subjects taking abiraterone should be monitored for hypertension, hypokalemia, and fluid retention at least once a month. Hypertension and hypokalemia should be controlled before and during treatment with abiraterone.

Subjects whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia should be closely monitored.

Adrenocortical Insufficiency: Adrenal insufficiency has been observed in patients taking abiraterone. Adrenocortical insufficiency has been reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Subjects should be monitored for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone. If clinically indicated, appropriate tests to confirm the diagnosis of adrenocortical insufficiency should be performed. Increased dosage of corticosteroids may be indicated before, during, and after stressful situations.

Hepatotoxicity: Abiraterone has been associated with severe hepatic toxicity, including fulminant hepatitis, acute liver failure, and deaths. Serum transaminases (ALT and AST) and bilirubin levels should be measured prior to starting treatment with abiraterone, every two weeks for the first three months of treatment, and every three weeks thereafter. Serum total bilirubin, AST, and ALT should be measured promptly if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the subject's baseline should prompt more

frequent monitoring. If at any time AST or ALT rises above 5 × ULN, or the bilirubin rises above 3 × ULN, interrupt abiraterone treatment and closely monitor liver function.

Re-treatment with abiraterone at a reduced dose level may take place only after return of liver function tests to the subject's baseline or to AST and ALT less than or equal to 2.5 × ULN and total bilirubin less than or equal to 1.5 × ULN.

Abiraterone must be permanently discontinued for subjects who develop a concurrent elevation of ALT greater than 3 × ULN and total bilirubin greater than 2 × ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

Refer to the most current local prescribing information appropriate to the respective study site location for additional details on warnings, precautions, possible AEs and management guidance for AEs associated with abiraterone.

For specific warnings and precautions regarding the use of prednisone please refer to the most current local prescribing information appropriate to the respective study site location.

6.6.4 Warnings, Precautions, and Management Guidelines for Adverse Events Associated with Enzalutamide

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in enzalutamide-treated patients from randomized placebo-controlled clinical trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension headache, and weight decreased.

Seizure: Seizure occurred in 0.4% of patients receiving enzalutamide. In patients with predisposing factors, seizures were reported in 2.2% of patients. Subjects should be advised of the risk of developing a seizure while receiving enzalutamide and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Enzalutamide must be permanently discontinued in subjects who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES): There have been reports of PRES in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue enzalutamide in subjects who develop PRES.

Hypersensitivity: Hypersensitivity reactions, including edema of the face, tongue, or lip have been observed with enzalutamide in clinical trials. Pharyngeal edema has been reported in post-marketing cases. Subjects who experience any symptoms of hypersensitivity should temporarily discontinue enzalutamide and promptly seek medical care. Enzalutamide must be permanently discontinued for serious hypersensitivity reactions.

Ischemic Heart Disease: In clinical studies, ischemic heart disease occurred more commonly in patients on the enzalutamide arm compared to the placebo arm. Subjects should be monitored for signs and symptoms of ischemic heart disease. Management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia should be optimized. Enzalutamide must be discontinued for Grade 3-4 ischemic heart disease.

Falls and fractures: Falls and fractures occurred in patients receiving enzalutamide. Subjects should be evaluated for fracture and fall risk. Subjects at risk for fractures should be monitored and managed according to established treatment guidelines, and the use of bone-targeted agents should be considered.

Embryo-Fetal Toxicity: The safety and efficacy of enzalutamide have not been established in females. Based on animal reproductive studies and mechanism of action, enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with enzalutamide and for 3 months after the last dose of enzalutamide. Enzalutamide should not be handled by females who are or may become pregnant

Refer to the most current local prescribing information appropriate to the respective study site location for additional details on warnings, precautions, possible AEs and management guidance for AEs associated with enzalutamide.

7 CONCOMITANT MEDICATION AND THERAPY

Concomitant medication taken by the subject from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment must be documented. Additionally, concomitant medications classified as immunosuppressive agents, including systemic corticosteroids, must be documented through 100 days after the date of the decision to discontinue study treatment.

Guidance on allowed, prohibited, and restricted therapies described in the subsequent sections must be followed throughout the study.

7.1 Allowed Therapies

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

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

- Bisphosphonates and/or denosumab can be used to control bone loss or hypercalcemia if the benefit outweighs the risk per the Investigator's discretion (Section 6.6.1.1.8).

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates and/or denosumab. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

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

- Topical, inhaled, intranasal, and/or intraarticular corticosteroids are allowed. For the experimental arm prophylactic systemic corticosteroids are allowed for control of infusion reactions and must be tapered to a dose level ≤ 10 mg/day of prednisone equivalent before next atezolizumab administration. If corticosteroids are initiated for the treatment of irAEs (except transfusion reactions), they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed unless otherwise specified in the AE management guidance (Section 6.6) or the atezolizumab Investigator's Brochure. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed. A short course of systemic steroids for acute medical conditions (such as worsening of COPD and gout flare) is allowed but steroids must be tapered to ≤ 10 mg/day oral prednisone or equivalent before the subsequent dose of atezolizumab. Local injections of steroids for local medical conditions may be allowed upon Sponsor's approval. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

- Individualized anticoagulation therapy with heparin or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances (for restrictions on oral anticoagulants, see Section 7.2):

- Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.

- At the time of the first dose of study treatment, therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed if the subject has no known brain metastasis, clinically significant hemorrhage, or complications from a thromboembolic event from the anticoagulation regimen or tumor, and the subject has been on a stable dose of the anticoagulant for at least 1 week before randomization.

- After first dose of study treatment, therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (eg, for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.6.1.1.4.

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

- Considerations for use of COVID-19 vaccine: At this time, there are limited data available for the use of COVID-19 vaccines in specific subsets of individuals such as the immunocompromised and cancer patients, including those receiving anticancer therapy such as cabozantinib, atezolizumab, and NHTs. The decision to proceed with vaccination

for subjects enrolled in this clinical study rests with the treating physician and the subject and should be taken after consideration of all safety precautions provided by the manufacturers of the vaccines and local health authorities. Please note, immunizations with live, attenuated COVID-19 vaccines or any experimental vaccines are not allowed. Exelixis will monitor all available information and provide additional guidance as appropriate.

Potential drug interactions with cabozantinib are summarized in Section 7.3.1. The drug interaction potential of atezolizumab is unknown (Section 7.3.2). Refer to the local prescribing information and the atezolizumab Investigator's Brochure. Potential drug interactions with abiraterone plus prednisone, and enzalutamide are summarized in Section 7.3.3 and Section 7.3.4, respectively.

7.2 Prohibited or Restricted Therapies

7.2.1 Prohibited or Restricted Therapies in Both Arms

The following therapies are prohibited in both arms until study treatment has been permanently discontinued or until otherwise specified:

- Any investigational agent or investigational medical device.
- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides [eg, radium-233], hormonal therapies, PARP inhibitors, other drugs or herbal products used specifically for the treatment of the cancer under investigation) with the exception of ongoing androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analog in subjects who have not undergone bilateral orchiectomy.

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

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established. If clinically unavoidable the Investigator should consult the Sponsor prior to the procedure for safety guidance, if possible.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).

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

7.2.2 Prohibited or Restricted Therapies in the Experimental Arm

In addition to the therapies listed in Section 7.2.1, the following therapies are prohibited in the experimental (cabozantinib and atezolizumab) arm until study treatment has been permanently discontinued or until otherwise specified:

- Oral anticoagulants (unless otherwise specified in Section 7.1) including, but not limited to, platelet inhibitors (eg, clopidogrel or ticagrelor), warfarin, dabigatran, betrixaban, and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines, until 4 weeks after cabozantinib has been permanently discontinued.

- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids except when atezolizumab has been permanently discontinued. See Section 7.1 for allowed corticosteroids.

- Live vaccines are prohibited while on study and until 5 months after last atezolizumab dose (eg, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin, yellow fever, varicella, and TY21a typhoid vaccines). The use of inactivated (killed) vaccines for the prevention of infectious disease is allowed.

- Metamizole (dipyrone) because of its potential for causing agranulocytosis (see Section 6.6.2.1.1).

In addition to the therapies listed in Section 7.2.1, the following therapies should be avoided in the experimental (cabozantinib and atezolizumab) arm until study treatment has been permanently discontinued or until otherwise specified:

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

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

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

7.2.3 Prohibited or Restricted Therapies in the Control Arm (NHT)

In addition to the therapies listed in Section 7.2.1, the following therapies should be avoided in the control (NHT) arm until study treatment has been permanently discontinued or until otherwise specified:

Abiraterone:

- Avoid concomitant strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) during abiraterone treatment.

- Avoid co-administration of abiraterone with CYP2D6 substrates that have a narrow therapeutic index (eg, thioridazine).

Enzalutamide:

- Avoid co-administration of enzalutamide with strong CYP2C8 inhibitors, as they can increase the plasma exposure to enzalutamide.

- Avoid co-administration of enzalutamide with strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. John's Wort), as they can decrease the plasma exposure to enzalutamide.

- Avoid co-administration of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (eg, phenytoin) and

CYP2C19 (eg, S-mephenytoin), as enzalutamide may decrease the plasma exposure of these drugs.

Please refer to the most current abiraterone, prednisone, and enzalutamide prescribing information appropriate to the respective site location for detailed information on prohibited or restricted therapies in the control arm. Potential drug interactions with abiraterone plus prednisone, and enzalutamide are summarized in Section 7.3.3 and Section 7.3.4, respectively.

7.3 Potential Drug Interactions

7.3.1 Potential Drug Interactions with Cabozantinib

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

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided (Appendix I). Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family

(eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib (Appendix I). Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

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

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

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

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, so fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the cabozantinib Investigator Brochure.

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

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

7.3.2 Potential Drug Interactions with Atezolizumab

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

7.3.3 Potential Drug Interactions with Abiraterone and Prednisone

In vitro studies showed that abiraterone is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Therefore, avoid concomitant strong CYP3A4 inducers during abiraterone treatment.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone 1,000 mg qd and prednisone 5 mg bid. Therefore, avoid co-administration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (eg, thioridazine) should be avoided.

In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone. Therefore, subjects should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone.

For additional details regarding potential drug interactions with abiraterone, refer to Appendix I and the most current prescribing information appropriate to the respective site location.

For information regarding potential drug interactions with prednisone, refer to the most current prescribing information appropriate to the respective site location.

7.3.4 Potential Drug Interactions with Enzalutamide

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Therefore, avoid co-administration of enzalutamide with strong CYP2C8 inhibitors.

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Therefore, avoid co-administration of strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's Wort) with enzalutamide.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Avoid concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (eg, phenytoin) and CYP2C19 (eg, S-mephenytoin), as enzalutamide may decrease their exposure.

For additional details on potential drug interactions with enzalutamide, refer to Appendix I and the most current prescribing information appropriate to the respective site location.

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

8.1.1 Adverse Events Definition

An AE is any untoward medical occurrence in a subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product.

All untoward events that occur after informed consent through the FU-1 visit (FU-2 visit for SAEs and certain other events [Table 8-1]) are to be recorded by the investigational site. At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report. The AE follow-up period is provided in Section 8.4 and further details are provided in Appendix J.

An AE does not include:

- A medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure.

- Pre-existing diseases or conditions present or detected before start of study drug(s) administration that do not worsen or increase in severity or frequency after the administration of study drug(s).
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for a planned procedure prior to study enrollment or for elective surgery for a condition that has not worsened on study; social and/or convenience admissions to grant families a respite in caring for a subject).
- Overdose of study drug(s) or concomitant medication without any signs or symptoms.

8.1.2 Adverse Events Causality Assessment

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

- **Not Related**: An event is assessed as not related to study drug(s) if it can be reasonably attributable to another cause such as subject's pre-existing medical history/risk factors, underlying disease, concurrent illness, or concomitant medications/therapies.
- **Related**: An event is assessed as related to study drug(s) when there is at least a reasonable possibility of a causal relationship between a suspected study drug(s) and an AE. The term "reasonable possibility" means that there are facts, evidence or arguments to support a causal relationship.

8.1.3 Adverse Events Grading

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the subject/event outcome or action criteria. All AEs will be assessed for severity using the National Cancer Institute (NCI) CTCAE v 5.0 guidelines. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 = Mild (event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities [eg, insomnia, mild headache])
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [eg, fever requiring antipyretic medication])

- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention)
- Grade 4 = Life threatening or disabling
- Grade 5 = Death

8.1.4 Laboratory Abnormalities and Other Clinical Investigations

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

8.2 Serious Adverse Events

8.2.1 Serious Adverse Events Definitions

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

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

- Results in death.
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event or reaction in which the subject was at immediate risk of death at the time of the event or reaction; it does not refer to an event or reaction which hypothetically might have caused death if it were more severe in the opinion of the Investigator.)
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization, except for the following:
    - A surgery or procedure that was planned before the subject entered the study and which is part of the planned study procedure.
    - Nonmedical reasons (eg, elective hospitalizations for social reasons or due to long travel distances or for prophylactic patient observation), in the absence of an AE.

- Results in significant incapacity or substantial disruption of the ability to conduct normal life functions.

- Is a congenital anomaly or birth defect.

- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2.2 Serious Adverse Events Reporting Rules

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

SAEs, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event by submitting the completed SAE report form and any other pertinent SAE information as indicated in the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites.

All SAEs that must be recorded in an eCRF or on an SAE Reporting form are as follows:

- All SAEs that occur after informed consent and through the FU-2 visit (ie, 100 [±14] days after the date of the decision to permanently discontinue study treatment, defined as the later of the date of the decision of the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by the subject).

- Any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs after the FU-2 visit.

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

SAEs that occur after informed consent through the FU-2 visit must also be recorded on the CRF page.

The minimum information required for the initial SAE reporting includes identity of Investigator, site number, subject number, the SAE term(s), the specification of any serious

criteria, severity (CTCAE grade), the Investigator's assessment of causal relationship between the event(s) and each study treatment, study treatment details (ie, start date, dosing, frequency, etc), and an event description.

Following the initial SAE reporting, the Investigator will continue to monitor the subject's clinical condition leading to the follow-up SAE reporting that may include updates on any performed investigations (eg, laboratory, imaging, consult notes), diagnostic evidence to support reported SAE term(s), medications or other therapeutic measures used to treat the event(s), action taken with the study treatment because of the event(s), and the outcome/resolution. Furthermore, the Investigator may be required to provide supplementary information such as hospital discharge summary, autopsy report, or death certificate, as requested by the Sponsor's Drug Safety personnel or designee.

When reporting SAEs, the following additional point should be considered:

- When the diagnosis of an SAE is known or suspected, the Investigator will report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.

8.2.2.1 Reporting Fatal/Death Cases

The term "Death" will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the Investigator must investigate the cause of death by collecting any available information (eg, clinical manifestation, date/time, location, death certificate, etc) and if an underlying diagnosis/etiology was identified, the SAE term should be amended accordingly. If an autopsy was performed, the autopsy report should be provided.

As a general rule, only one SAE should be considered as the primary cause of death (per investigator's opinion) and reported with an outcome of "Fatal," serious criterion of "Death" and severity Grade 5. Any other serious events ongoing at the time of death should be reported as non-fatal SAEs. All deaths should be recorded in the AE and Death CRF as AEs, even if they occur after the follow-up period.

8.2.2.2 Reporting Disease Progression Cases

It is anticipated that during this study a proportion of subjects will experience underlying cancer progression on or after discontinuation of study treatment. In this context, subjects may

experience multiple clinical manifestations (eg, asthenia, general physical health deterioration, ascites, increasing edema, dyspnea, bleeding, multi-organ failure, etc) that may be attributed to the underlying cancer progression. In general, any observed clinical manifestations meeting at least one SAE criterion should be reported as individual SAE terms. Relevant information on the underlying cancer progression should be provided in the SAE description and be recorded in the the CRF. Reporting of the underlying "prostate cancer progression" as an SAE term should generally be avoided and should be reserved for fatal prostate cancer progression or situations when the clinical manifestation is non-specific (eg, general physical health deterioration) or in case of a documented terminal underlying disease without another clear cause of death (eg, for fatal cancer progression occurring in hospice).

8.2.3 Regulatory Reporting

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with applicable global and/or local regulatory requirements.

In subjects with advanced cancer, natural progression of malignancy may occur; hence any progression of underlying malignancy, for which the study drug(s) are administered, is being considered an expected event for regulatory reporting purposes.

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

Updates to the protocol, Investigator's Brochure (IB), and informed consent due to new safety signals will be performed per regulatory requirements. Events that require notification of significant safety information may be communicated by a Dear Investigator (or similar) letter to participating sites and relevant health authorities with a subsequent update of protocol, Investigator's Brochure, and informed consent.

8.3 Adverse Events of Special Interest for Atezolizumab

Adverse events of special interest (AESIs) consist of immune-mediated AEs associated with ICIs, cases of potential drug-induced liver injury (DILI), and suspected transmission of an infectious agent by the study treatment (Table 8-1).

AESIs will be reported to the Sponsor or designee via eCRF or using the SAE reporting form irrespective of whether the event is serious or nonserious; all AESIs must be reported within 24 hours using the SAE reporting process as described in Section 8.2.2.

Guidance for management of immune-mediated AEs associated with atezolizumab is provided in Section 6.6.2 and can also be found in the local prescribing information and Investigator's Brochure for atezolizumab.

Table 8-1: Adverse Events of Special Interest for Atezolizumab

Event
• Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN o Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
• Suspected transmission of an infectious agent by the study treatment, as defined below o Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
• Systemic lupus erythematosus
• Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
• Nephritis
• Ocular toxicities (eg, uveitis, retinitis, optic neuritis)
• ≥ Grade 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
• Vasculitis
• Autoimmune hemolytic anemia
• Severe cutaneous reactions (eg, Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis)
• Grade ≥ 3 diarrhea
• Myelitis
• Facial paresis

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.

8.3.1 General Information on Immune-Related Adverse Events

The immune-modulating properties of immune checkpoint-inhibitors, such as the anti-PD-L1 antibody atezolizumab, are able to unbalance the immunologic tolerance and generate a subset of AEs (called irAEs) with an autoimmune inflammatory pathomechanism. IrAEs may involve every organ or tissue (Michot et al 2016). Most irAEs occur within the first 12 weeks of

exposure to ICIs but some may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs are fatigue, fever, and chills. Organ-specific irAEs include dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively unspecific symptoms. Additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), T4 and TSH (pituitary-thyroid function), luteinizing hormone (LH) and follicle-stimulating hormone (FSH; pituitary-gonadal function), adrenocorticotropic hormone (ACTH) and cortisol (pituitary-adrenal function).

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

8.4 Follow-Up of Adverse Events

Nonserious AEs (see below for AESIs [Table 8-1]) are to be recorded in the CRF through the FU-1 visit. The status of unrelated SAEs that are ongoing after the date of the decision to discontinue study treatment will be documented through the FU-2 visit.

All AESIs (regardless of seriousness) and all related SAEs that are ongoing at the FU-2 visit, and AEs assessed as related that led to study treatment discontinuation that are ongoing at the FU-2 visit are to be followed until:

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

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

All deaths should be recorded in the AE and Death CRF as AEs, even if they occur after the follow up period.

8.5 Other Safety Considerations

8.5.1 Pregnancy

Use of highly effective methods of contraception (Appendix E) is very important during the study and must continue for 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm). Furthermore, subjects must refrain from donating sperm and are required to use condoms in order to avoid transmission of study treatment in semen for the same periods described above. If a partner of a subject becomes pregnant during the study, the Sponsor will ask the pregnant partner to consent to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth.

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

Subjects should seek advice and consider fertility preservation before receiving study treatment.

8.5.2 Special Situation Reporting

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

A Medication Error Notification Form should be completed and sent to the Sponsor following any suspected medication error.

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

Please refer to the cabozantinib Investigator's Brochure for additional management recommendations for an overdose of cabozantinib, and to the most current prescribing

information appropriate to the respective site location for management of overdoses of abiraterone, prednisone, or enzalutamide.

9 STATISTICAL CONSIDERATIONS

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

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all subjects who are randomized, regardless of whether any study treatment or the correct study treatment is received.

9.1.2 PFS Intent-to-Treat Population

The first 324 subjects that are randomized (based upon Greenwich Mean Time randomization date/time values) to the experimental arm or control arm will be considered as the PFS Intent-to-Treat (PITT) population. The population may be extended to the first 400 subjects randomized if a review of accumulating events suggests that the number of events required may not (or may take much longer than expected to) be reached (due to permanent censoring) among the first 324 subjects originally planned.

9.1.3 Safety Population

The Safety population will consist of all subjects who receive any amount of study treatment. Analyses based on the Safety population will be performed according to the actual treatment received. Data handling rules for subjects who received incorrect study treatment will be described in the SAP.

9.2 Primary Efficacy Endpoints

The multiple-primary efficacy endpoints are duration of PFS per RECIST 1.1 and OS.

9.2.1 Definitions

9.2.1.1 Duration of Progression Free Survival

Duration of PFS is defined as the time from randomization to the earlier of either radiographic PD per RECIST 1.1 or death due to any cause. The definition of disease progression and censoring rules for the primary analysis are described in Section 9.2.2.1.

9.2.1.2 Duration of Overall Survival

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

9.2.2 Primary Analysis

9.2.2.1 Progression-Free Survival

The primary analysis of PFS is event-driven and will be conducted after at least 202 events have been observed in the PITT population (see Section 9.1.2). It is designed to include progression events as determined per RECIST 1.1 by the BIRC. Clinical deterioration determined by the Investigator will not be considered progression events.

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

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

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

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

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided 0.002 level of significance. The stratification factors will be the same as those used to stratify the randomization (see Section 3.4).

The median duration of PFS and the associated 95% and 99.8% CIs for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% and 99.8% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

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

9.2.2.2 Overall Survival

The primary analysis of OS is event-driven and will be conducted after at least 340 deaths have been observed in the ITT population (Section 9.1.1).

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

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

Two interim analyses of OS are planned at approximately the 32% and 76% information fractions. Details are provided in Section 9.8.

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

9.2.2.3 Supportive Analyses

Supportive (sensitivity) analyses will be conducted using all PFS events and subjects in the ITT population at the time of the primary PFS analysis. Additional sensitivity analyses of PFS will be defined in the SAP using alternative event definitions (such as PFS per PCWG3) and censoring schemes to account for partial or completely missing assessments, address bias due to tumor assessment timing, and to evaluate the impact of potentially informative censoring. These analyses will be performed using the same statistical methods described for the primary analysis.

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

9.3 Secondary Efficacy Endpoint

Formal hypothesis testing is planned for the secondary efficacy endpoint of ORR.

9.3.1 Definitions

9.3.1.1 Objective Response Rate

The secondary endpoint is ORR and is defined as the proportion of subjects for whom the best overall response at the time of data cutoff is a CR or PR as assessed by the BIRC per RECIST 1.1, which is confirmed by a subsequent visit ≥ 28 days later. Subjects who do not have any post-baseline tumor assessments will be counted as non-responders

9.3.2 Objective Response Rate

ORR will be tested using the Cochran-Mantel-Haenszel test (stratified by the randomization stratification factors) at the 2-sided α level (the α level will be defined per Section 9.5) in the ITT population with measurable disease at baseline, provided the null hypothesis for OS is rejected in favor of the experimental arm (cabozantinib + atezolizumab) at the interim or final OS analysis. Point estimates of ORR and corresponding CI estimates calculated by exact methods will be provided.

9.4 Additional Endpoints

Details of the planned analyses of these endpoints will be provided in the SAP:

- PSA response rate
- Duration of radiographic response per RECIST 1.1 (per Investigator and BIRC)
- Duration of PFS per PCWG3 per BIRC, defined as the time from randomization to the earlier of radiographic PD based on CT/MRI per RECIST 1.1, bone disease progression based on bone scans per PCWG3, or death due to any cause

- Time to PSA progression
- Time to SSE
- Time to pain progression, defined as earlier of:
    - ≥ 2 point increase in pain score compared to baseline in an 11-point NRS measuring worst pain in the last week
    - New or increased analgesic use from baseline (for analgesics taken for at least 7 consecutive days)
- Time to chemotherapy
- Health care resource utilization
- Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health as assessed by the EuroQol Health questionnaire EQ-5D-5L and EORTC questionnaire QLQ-C30
- Safety as assessed through the evaluation of adverse events (AEs), including immune-related adverse events (irAEs)
- Pharmacokinetics (PK) of cabozantinib given in combination with atezolizumab
- Immunogenicity of atezolizumab given in combination with cabozantinib
- Correlation of immune cell, tumor cell, and plasma biomarker analyses with clinical outcomes

9.5 Control of Type I Error

Inflation of Type 1 error associated with multiple primary endpoints will be controlled by a closed testing procedure that employs modified Bonferroni and fallback methods. The study-wise 2-sided alpha of 0.05 will be nominally divided between multiple primary endpoints PFS (0.002) and OS (0.048) with pre-specified alpha levels passed from significant endpoints to those to be tested next per the pre-specified testing strategy.

Two interim analyses of OS are planned (see Section 9.8). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending function.

Inflation of Type 1 error associated with testing the secondary endpoint of ORR will be controlled by applying a hierarchical testing procedure. ORR will only be tested if the null hypothesis for OS is rejected in favor of the experimental arm (cabozantinib + atezolizumab).

Testing and alpha reallocation will proceed as follows:

At the primary PFS analysis, test PFS at 0.002 level. Then:

1. If PFS is significant, re-allocate 0.002 alpha to OS and conduct the planned interim and final analyses of OS per LD-OF at 0.05 allocated alpha
    a. If OS is not significant at any analysis, procedure ends
    b. If OS is significant at any analysis, re-allocate its 0.05 alpha to ORR and test ORR at 0.05
2. If PFS is not significant, conduct the planned interim and final analyses of OS per LD-OF at 0.048 allocated alpha
    a. If OS is not significant at any analysis, procedure ends
    b. If OS is significant at any analysis, re-allocate its 0.048 alpha to ORR and test ORR at 0.048
        i. If ORR is significant at 0.048, retest PFS at 0.05
        ii. If ORR is not significant at 0.048, procedure ends

The median duration of PFS and the associated 95% and 99.8% CIs for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% and 99.8% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

9.6 Safety Analyses

All safety analyses will be performed using the Safety population. No formal statistical comparisons between the two treatment arms are planned.

9.6.1 Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The Investigator will classify the severity of AEs using the CTCAE v5 and will judge each event to be “not related” or “related” to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after date of first dose of study treatment. Only TEAEs with an onset date through the 30-day post-treatment follow-up visit (100-day post-treatment follow-up visit for SAEs and AESIs consisting of conditions listed in Table 8-1) will be tabulated in summary tables.

The frequency and percentage of subjects with TEAEs will be tabulated for overall incidence by system organ class and/or preferred term by treatment arm. Related TEAEs, serious TEAEs, related serious TEAEs, high-grade TEAEs, Grade 5 TEAEs, and TEAEs resulting in study

treatment discontinuation will be similarly summarized. Summaries by worst reported severity for each event within a subject will also be provided.

At each level of summarization, a subject will be counted only once for each AE preferred term he/she experiences within that level (ie, multiple episodes of events with the same preferred terms will be counted only once).

All reported subject deaths will be summarized by treatment group, cause of death, and relationship to study treatment.

9.6.2 Laboratory Test Results

Laboratory test results will be summarized by treatment group to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

9.6.3 Other Safety Endpoints

Changes or shifts from baseline in vital signs, performance status, and QTc interval will be summarized by treatment group.

The number of subjects experiencing dose reduction (cabozantinib and NHTs only), interruption, and/or discontinuation due to an AE will be provided.

Concomitant medications will be standardized using the World Health Organization drug dictionary and summarized by class and preferred term.

9.7 Power and Sample Size

The study is designed to provide adequate power for comparisons of both PFS and OS endpoints between the experimental (combination regimen) and control (NHT) arms. Compared with OS, a smaller sample size is needed to provide reasonable power for PFS. As a result, the number of events necessary to trigger the primary analysis of PFS could be reached before the study is fully accrued, and PFS events could be biased toward shorter progression times were PFS evaluated in the larger sample size required for OS. Thus, to reduce bias toward shorter progression times, this study employs a “trial within a trial” design (Hessel 2016) to allow longer, more robust PFS follow-up among fewer subjects than the total required for OS. Futility and interim analyses of PFS are not planned.

For PFS, a total of 202 events in the first 324 subjects randomized in the combination and second NHT control arms provide the study with 90% power for a 2-sided log-rank test with a 0.002 level of significance to detect a hypothesized true HR of 0.54. Assuming an exponential

distribution of PFS, this corresponds to an 85% increase in median PFS from 4 months to 7.4 months. In the current design, the minimum observed effect that would result in statistical significance for PFS is a HR of 0.65, a 55% improvement in median PFS from 4 to 6.2 months.

For OS, a total of 340 deaths among all 580 subjects randomized in the combination and second NHT arms are required to provide 90% power to detect an HR of 0.70 using the log-rank test and a 2-sided significance level of 0.048. Assuming an exponential distribution for OS, this corresponds to a 43% increase in median survival from 14 months to 20 months. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS is an HR of 0.80, a 25% improvement in median from 14 to 17.5 months.

Two interim analyses of OS are planned and will include all subjects randomized to combination and second NHT control arms at the time of each analysis. The first interim analysis of OS will be conducted at the time of primary analysis of PFS. This is expected to occur at approximately the 32% information fraction for OS. The second interim analysis of OS is planned at approximately the 76% information fraction. Inflation of Type 1 error associated with these interim analyses will be controlled using LD-OF alpha-spending functions based upon a total alpha allocation for OS that depends upon whether the PFS result is significant.

With an average accrual rate of ~24 subjects per month (3 subjects per month for 5 months, 26 subjects per month from 6 to 15 months, and 37 subjects per month from month 16 onward) and using a 1:1 treatment allocation ratio among the experimental and control arms, a total of 580 subjects (290 subjects in each arm) are required to observe the required number of events within the planned study duration (approximately 24 months accrual; approximately 21 months to observe the required PFS events and approximately 37 months to observe the required deaths for OS). These estimates are based upon the statistical assumptions, adjusted to accommodate the time required for all study sites to be activated and for subject recruitment to reach full potential. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. The estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation.

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

An overview of the endpoints and operating characteristics is shown in Table 9-1:

Table 9-1: Summary of Endpoint Analysis

Accrual per month	Max 37 after 16 months*	
Randomization allocation	1:1	
Endpoint:	**PFS: Primary Endpoint**	**OS: Primary Endpoint**
Power	90%	90%
Alpha allocated (2-sided)	0.002	0.048
# of interim analyses (approximate information fraction)	0 (NA)	2 (32%, 76%)
Assumed median control vs experimental (months)	4 vs 7.4	14 vs 20
Assumed HR	0.54	0.70
Number of events	202	340
N for analysis	324 (PITT population)	580 (ITT Population)
Time to enroll (months)	16	24
Time to trigger event (months)	21	37
Maximum HR to reject Ho (experimental median in months)	0.65 (6.2)	0.80 (17.5)

Ho, null hypothesis; HR, hazard ratio; ITT, intent-to-treat; NA, not applicable; OS, overall survival; PITT, PFS intent-to-treat; PFS, progression-free survival

* Accrual: 3/month until 5 months, 26/month from 6-15 month and 37/month from 16 months onward.

9.8 Interim Analyses

The number of events required to evaluate OS is based upon assumptions currently available and provides high power to detect the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the trial early if the treatment benefit of the experimental arm is larger than expected, potentially allowing the new regimen to become available sooner to this patient population.

Two interim analyses of OS are planned and will include all subjects randomized to combination and second NHT control arms at the time of each analysis. The first interim analysis of OS will be conducted at the time of primary analysis of PFS. This is expected to occur at approximately the 32% information fraction for OS. The second interim analysis of OS is planned at approximately the 76% information fraction. Inflation of Type 1 error associated with these interim analyses will be controlled using LD-OF alpha-spending functions based upon a total alpha allocation for OS that depends upon whether the PFS result is significant.

Details and boundaries for testing OS at interim and the final analyses are shown in Table 9-2.

Table 9-2: Boundaries for Interim and Final Analyses of Overall Survival

			PFS is significant		PFS is not significant	
OS alpha			0.05		0.048	
OS analysis information fraction	Approximate # of events	Analysis Time	Critical p-value	Max HR to reject	Critical p-value	Max HR to reject
32%	109	21	0.00015	0.484	0.00013	0.481
76%	258	30	0.020	0.748	0.019	0.747
100%	340	37	0.044	0.804	0.042	0.802

HR, hazard ratio; PFS, progression-free survival; OS, overall survival

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

If the null hypothesis of no difference in OS is rejected at a planned interim OS analysis in favor of the experimental arm (cabozantinib + atezolizumab), no subsequent testing of OS is planned.

10 OTHER ANALYSES

10.1 Pharmacokinetic Analysis

The plasma concentration of cabozantinib will be analyzed by designated laboratory using a validated bioanalytical method. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit. Where appropriate, these data may be combined with data from other studies as part of a meta-analysis (ie, population PK analysis). The effect of cabozantinib exposure on biomarkers, clinical safety parameters (eg, selected AEs) or clinical response may also be explored.

Serum concentrations of atezolizumab will also be measured. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit.

10.2 Immunogenicity Analyses

Results of anti-drug antibody (ADA) testing (immunogenicity) will be summarized overall as the number of subjects with ADA at any time point. The association between human ADA incidence, PK, and efficacy and/or safety outcomes may be explored.

10.3 Biomarker Analyses

Analyses may include correlation of biomarker data (eg, biomarker expression levels, mutation status) with clinical response.

11 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the Investigator. Authorized study site personnel will enter data directly into a computerized eCRF database (ie, EDC system). Study databases will be subject to electronic and manual quality assurance procedures.

12 STUDY COMMITTEES

12.1 Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects and will not be authors on publications resulting from the study. IDMC members will be selected for their expertise in oncology.

This IDMC will convene regularly. The primary responsibilities of the IDMC are to:

- Review the accumulating safety data on a regular and an ad hoc basis
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety and efficacy data

Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings. To allow the evaluation of safety in the context of potential benefit, OS data (including Kaplan-Meier curves) may be reviewed by the IDMC at the time of safety summary reviews. The IDMC will have access to subjects' individual treatment assignments.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.

The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to the Sponsor's senior management.

Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate IDMC charter.

12.2 Blinded Independent Radiology Committee (BIRC)

A BIRC will be established to evaluate tumor scans and prior radiation history data of trial subjects in a central, blinded, and independent fashion (see also Section 5.6.6.3). The BIRC will be comprised of board-certified radiologists who will determine radiographic response and progression following randomization. Additional imaging results may be requested by the Sponsor for BIRC review.

Additional details regarding BIRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the BIRC Charter.

12.3 Clinical Steering Committee (CSC)

The Clinical Steering Committee consists of physicians who have an expertise in treating patients with prostate cancer. The CSC will provide critical scientific guidance including, but not limited to, protocol design and implementation and interpretation of clinical study results.

12.4 Corporate Safety Governance

The Sponsor has an established internal safety governance structure which oversees the monitoring of the safety and benefit-risk profile for all investigational products on an ongoing basis across all ongoing company-sponsored clinical studies.

13 ETHICAL ASPECTS

13.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (June 2017) and remain consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study

complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

13.2 Informed Consent

Sample ICFs will be supplied to each site. The Sponsor or its designee must review any proposed deviations from the sample ICF. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject. If applicable, the ICF will be provided in a certified translation of the subject's language.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, will be given a copy of the revised form, and must give their consent to continue in the study.

13.3 Institutional Review Board/Ethics Committee (IRB/EC)

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The Investigator will send a letter or certificate of IRB/ EC approval to the Sponsor (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

13.4 Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all research samples. If a subject requests destruction of their tissue and blood samples, the Sponsor will

make every attempt to destroy the samples. The Sponsor will notify the Investigator in writing that samples have been destroyed.

14 CONDITIONS FOR MODIFYING THE PROTOCOL

If deemed necessary, protocol modifications will be prepared, reviewed, and approved by the Sponsor representatives.

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

15 CONDITIONS FOR TERMINATING THE STUDY

The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS (experimental vs control arm) in either of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results).

The Sponsor reserves the right to terminate the study, and Investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, the Sponsor and the Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

16 STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORD KEEPING

16.1 Investigator's Files and Retention of Documents

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

The investigator's study file will contain the protocol and protocol amendments, CRFs (site contents will be converted to digital storage format [eg, compact disc] for archiving), query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subjects' clinical source documents to record key efficacy and safety parameters independent of the CRFs include the subjects' hospital/ clinic records; physician's and nurse's notes; the appointment book; original laboratory, ECG, electroencephalogram, x-ray, pathology and special assessment reports; signed ICFs; consultant letters; and subject screening and enrollment logs.

The Investigator must keep these two categories of documents on file for the maximum period required by applicable regulations and guidelines, institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. After that period, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirements at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

16.2 Source Documents and Background Data

Upon request, the Investigator will make available for review to the Sponsor any required background data from the study documentation or clinic records. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

16.3 Audits and Inspections

The Investigator ensures that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Sponsor's Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

16.4 Case Report Forms

The term "case report form" (CRF) includes EDC screens or forms for studies that utilize EDC. For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and required by the CRFs are to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or a designee electronically, eg, laboratory data). Data from some procedures required by the protocol, such as physical examinations, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and

assessments may be performed as part of the Investigator's institution or medical practice standard of care. Otherwise, data for unscheduled or additional assessments are to remain in the subject's medical record and are not to be recorded on CRFs unless specifically requested.

The CRF casebook must be completed and signed by the Investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

The Sponsor's data management personnel (or designees) may, in specific circumstances, modify study data – without changing the meaning of the data – to ensure the dataset complies with conventions required for successful data extract, thesaurus coding, or uniform reporting and does not cause these processes to fail. Examples of these administrative changes include:

- Substitution of non-standard ASCII characters (codes 128-255) or deletion of carriage returns (code 13) that are incompatible with the SAS XPT file format (eg, accented letters replaced with non-accented ones; e for é)
- Splitting multiple verbatim AE terms into multiple records (eg, "nausea and vomiting" to separate records for "nausea" and "vomiting")
- Reformatting failed eligibility criteria numbers for uniformity or specificity (eg, changing "2 a" to "2A"; or "2" to "2A" based on corroborating evidence from the clinical database)
- Changing cause of death from "unknown" to "unknown cause of death" to facilitate coding in the MedDRA thesaurus

Such changes follow a pre-defined documented process and can be clearly identified in the database audit trial. By participating in this study, investigators agree that such administrative changes are permissible without their specific prior approval. A list of all specific changes made can be provided to investigators upon request at any time.

17 MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other

pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor is to have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

18 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

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

19 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In the event that the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of the Investigator(s) or other representatives of the study site(s) as named author(s) shall be determined in accordance with Sponsor policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

20 COMPLIANCE WITH DATA PROTECTION LAWS

The Sponsor, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors
- ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial
- implementing the pseudonymisation and encryption of personal data, as appropriate

- implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services
- implementing network, application, database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident
- logging of security events/incidents in information systems
- implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents
- ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up
- a process for regularly testing, assessing and evaluating the effectiveness of technical and organisational measures for ensuring the security of the processing
- implementing procedures to capture within reasonable time-manner any personal data breach occurred
- implementing procedures and practices for securing destruction of paper documents containing personal data
- implementing business continuity procedures ensuring that THE SPONSOR can continue to provide services through operational interruption

All locations, personnel and information systems that are used to perform services for the Study will be covered.

The Sponsor will ensure technical and organizational security measures described above, are regularly reviewed and updated to take into account any evolution on technological developments.

The Sponsor may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, the Sponsor, by means of internal measures and imposed contractual clauses to the selected sub-contractors, ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, the name of the patient will neither be asked for, nor recorded by the the Sponsor. An identification number will be allocated to each patient registered in the Study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient. In order to avoid identification errors, the site number will also be reported on the case report forms.

Monitors acting on behalf of the Sponsor will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the Study. Staff involved in the performance of this task is bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

The Sponsor has put in place a functional process of reporting of any data breach occurring at the Sponsor's or its sub-contractor's facilities and premises. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by the the Sponsor (via clinical Study site).

21 REFERENCES

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APPENDICES

Appendix A: Screening Assessments

To determine subject eligibility as stipulated in Section 4, subjects will undergo required screening evaluations as outlined in this appendix and described in Section 5.6. Qualifying screening assessments must be performed within 21 days before randomization unless otherwise stated. If there is a change in clinical status after screening and prior to randomization, these assessments are to be repeated as clinically indicated and deemed acceptable prior to randomization. Study eligibility is based on a subject meeting all inclusion criteria and no exclusion criteria at screening.

Screening Assessments:

Assessment	Screening[a] (before randomization)
Informed consent	X[b]
Demographics, medical and cancer history	≤ 28 days
Physical examination + weight + height	≤ 21 days
Vital signs	≤ 21 days
ECOG	≤ 21 days
12-lead ECG	≤ 21 days
Hematology, chemistry, PSA, serum testosterone, PT/INR, PTT, thyroid function tests, UPCR including components[c, g]	≤ 21 days
Urinalysis[c]	≤ 21 days
Hepatitis screening[d]	≤ 21 days
HIV testing (if required by local regulations)	≤ 21 days
Tumor assessment: Chest CT, Abdomen/Pelvis CT or MRI, technetium bone scan	≤ 28 days
Tumor assessment: Brain MRI (or CT) if clinically indicated	≤ 28 days
Tumor assessment: Bone CT if clinically indicated	≤ 28 days
Analgesic Use[e]	Document those taken within 28 days before randomization.
Archival tumor tissue (if available)	X[f]
Concomitant medications	Document those taken within 28 days before randomization.
Adverse events	Document Serious AEs and AESIs from informed consent.

AE, adverse event; AESI, adverse of special interest; CT, computerized tomography; EC, ethics committee; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRB, institutional review boards; MRI, magnetic resonance imaging; PSA, prostate specific antigen; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; RNA, ribonucleic acid; UPCR, urine protein/creatinine ratio

[a] Results of screening assessments must be reviewed before randomization to confirm subject eligibility.

[b] Informed consent may be obtained more than 28 days prior to randomization but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies.

[c] See Section 5.6.5 and the Laboratory Manual for more detailed information on laboratory assessments

[d] Hepatitis B surface antigen and Hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive).

[e] Baseline dose will be determined for analgesics taken for at least 7 consecutive days during screening.

[f] Available archived tumor tissue can be provided during the screening evaluation period up to week 7. If archival tumor tissue is not available, a fresh tumor biopsy may be obtained prior to first dose of study treatment.

[g] Direct and indirect bilirubin assessments are not required when the total bilirubin is normal or low.

Appendix B: Schedule of Assessments from Randomization Onwards

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety are to occur during routine safety visits (RSVs). Routine Safety Visit 1 (RSV1) is to occur no more than 72 hours prior to the first dose of any study treatment(s). First dose of study treatment(s) is to occur within 3 days after randomization.

After RSV1, subsequent RSVs are required at least every 3 weeks (± 3 days) (ie, no more than 3 weeks [± 3 days] apart). If there is a dose delay for any study treatment, subjects must return to the site for an RSV at least every 3 weeks (± 3 days) during the dose delay and follow up with additional unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for resumption of study treatment. See the schedule below for safety assessments to be performed at each RSV.

In the experimental arm, an RSV is required within 72 hours prior to each planned infusion of atezolizumab (vital signs must be assessed within 60 min prior to initiation of the infusion), even if fewer than 3 weeks have elapsed since the last RSV. Once atezolizumab is restarted after a treatment delay, RSVs are to occur at least every 3 weeks (± 3 days) thereafter (ie, RSV schedule resets on date of infusion).

Imaging (CT, MRI, TBS), PSA, HRQOL, and pain assessments are to be performed at protocol-defined intervals based on the date of randomization; all subsequent time points for these assessments will occur at a defined time interval and will not be modified as a result of modifications or discontinuations of treatment administration. After randomization, these assessments are to be performed every 9 weeks (± 7 days) through Week 28 and then every 12 weeks (± 7 days). See Sections 5.6.6.1, 5.6.7, 5.6.8, and 5.6.9, respectively, for details.

Unscheduled visits for safety evaluations are allowed at any time (see Section 5.5).

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

The following are reminders for procedures and assessments during the treatment period:

- Cabozantinib and second NHTs are dosed once daily (prednisone is dosed twice daily).
- Doses of atezolizumab should be administered every 3 weeks and no more frequently than every 19 days (see Section 6.2.3.1). If atezolizumab administration is not delayed for AE management, it should be administered within 24 days of the prior atezolizumab dose. Atezolizumab dosing can be delayed for up to 12 weeks, after which the Sponsor should be contacted to discuss potential treatment continuation.
    - Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented by the Investigator. The Sponsor is available to advise as needed.
- Specific laboratory tests must be performed at an RSV and evaluated within 72 hours prior to each administration of atezolizumab (see Section 5.6.5). These assessments are not required prior to the first dose if there has been no change in subject's clinical status since screening.
- Safety will be assessed on a schedule based on date of first dose as described above. RSVs must occur at least every 3 weeks (± 3 days), even if there is a study treatment dose delay. In the experimental arm, an RSV is required within 72 hours prior to each planned infusion of atezolizumab (vital signs must be assessed within 60 min prior to initiation of the infusion), even if less than 3 weeks have elapsed since the last RSV. Once atezolizumab is restarted after a treatment delay, RSVs are to occur at least every 3 weeks (± 3 days) thereafter. Unscheduled visits may occur at any time.
- For subjects receiving abiraterone plus prednisone, serum ALT, AST, and total bilirubin assessments (LFTs) are to be performed every 2 weeks for the first 12 weeks of treatment, in addition to at each RSV (see schedule below). If an LFT visit coincides with an RSV, duplicate LFTs do not need to be performed. After the first 12 weeks of treatment, LFTs will continue to be performed at each RSV.
- Radiographic tumor assessments are to be performed every 9 weeks (± 7 days) through Week 28 and then every 12 weeks (± 7 days) relative to the date of randomization and irrespective of the dates of RSVs. PSA, HRQOL, and pain assessments after RSV1 are to occur with scheduled radiographic tumor assessments.

- PK, anti-drug antibodies (ADA), and biomarker sample collection schedules are per schedule of assessments.

Assessment	Post-Randomization											Post-Treatment	
	RSV1 (To occur no more than 72 hours prior to 1st dose.)	After RSV1, subsequent RSVs are required at least every 3 weeks (ie, no more than 3 weeks apart), even if treatment is held. For atezolizumab dose delays: an RSV is required within 72h prior to each planned infusion, resetting next RSV interval									Unscheduled Visit[o]	FU-1[p]	FU-2[q]
		RSV2 (±3 Days)	RSV3 (±3 Days)	RSV4 (±3 Days)	RSV5 (±3 Days)	RSV6 (±3 Days)	RSV7 (±3 Days)	RSV8 (±3 Days)	RSV9 (±3 Days)	RSV10 through RSV 17 (±3 Days)	Each RSV after RSV17 until treatment is discontinued (±3 Days)		30-Day Post Treatment Follow-Up (+14 Days)	100-Day Extended Follow-Up (±14 Days)
Directed physical examination + weight (Section 5.6.2)	pre-dose	X	X	X	X	X	X	X	X	X	X	Perform assessment(s) as clinically indicated (see Section 5.5)	X	X
Vital signs (Section 5.6.3)	pre-dose	X	X	X	X	X	X	X	X	X	X		X	X
ECOG performance status (Section 5.6.2)	pre-dose	X	X	X	X	X	X	X	X	X	until imaging discontinued			
12-lead ECG[a, c] (Section 5.6.4)	pre-dose	X	X		X		X		X	Every 4 RSVs eg, RSV13, RSV17, etc				
Hematology, chemistry, PT/INR, PTT, urinalysis[b,c,t] (Section 5.6.5)	pre-dose	X	X	X	X	X	X	X	X	X	Experimental Arm: Every RSV Control Arm: Every 2 RSVs eg, RSV17, RSV19, etc		X	
Thyroid function tests (TSH and free T4)[b, c] (Section 5.6.5)	pre-dose	X	X	X	X				X	Every 4 RSVs eg, RSV13, RSV17, etc			X	
Additional serum ALT, AST, and total bilirubin tests (subjects receiving abiraterone/prednisone)[t] (Section 5.6.5)	pre-dose	For subjects receiving abiraterone plus prednisone, serum ALT, AST, and total bilirubin assessments (LFTs) are to be performed on Week 3 Day 1 (W3D1 [± 3 days]), W5D1 (± 3 days), W7D1 (± 3 days), W9D1 (± 3 days), W11D1 (± 3 days), and W13D1 (± 3 days), in addition to at each RSV[s]. After W13D1, LFTs will continue to be performed at each RSV.											X	
UPCR (including components)[b, c, d] (Section 5.6.5)	pre-dose	X	X	X	X	X	X	X	X	X	Every 2 RSVs eg, RSV17, RSV19, etc		X	
Analgesic use assessments[e] (Section 5.6.9)	X	X	X	X	X	X	X	X	X	X	X		X	X
Symptomatic skeletal events assessments[f] (Section 5.6.10)	X	X	X	X	X	X	X	X	X	X	X		X	X

Assessment	Post-Randomization												Post-Treatment	
	RSV1 (To occur no more than 72 hours prior to 1st dose.)	**After RSV1, subsequent RSVs are required at least every 3 weeks (ie, no more than 3 weeks apart), even if treatment is held. For atezolizumab dose delays: an RSV is required within 72h prior to each planned infusion, resetting next RSV interval**										**Unscheduled Visit[o]**	**FU-1[p]**	**FU-2[q]**
		RSV2 (±3 Days)	**RSV3 (±3 Days)**	**RSV4 (±3 Days)**	**RSV5 (±3 Days)**	**RSV6 (±3 Days)**	**RSV7 (±3 Days)**	**RSV8 (±3 Days)**	**RSV9 (±3 Days)**	**RSV10 through RSV 17 (±3 Days)**	**Each RSV after RSV17 until treatment is discontinued (±3 Days)**		**30-Day Post Treatment Follow-Up (+14 Days)**	**100-Day Extended Follow-Up (±14 Days)**
Health Care Utilization[g] (Section 5.6.11)	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant medications (Section 7)	Document from 28 days before randomization through 30 days after decision to discontinue study treatment. Concomitant medications classified as immunosuppressive agents, including systemic corticosteroids, must be documented through 100 days after the date of the decision to discontinue study treatment.													
Adverse events (Section 8)	Document new or worsening events (see Section 8.1). Adverse events information will be collected at all study visits and may also be collected at any time over the phone or by spontaneous subject report. Certain AEs and all SAEs that are ongoing 30 days after last dose of study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible (see Section 8.4).													
Serum PSA (Section 5.6.7)	PSA assessments will occur with scheduled imaging: every 9 weeks ± 7 days through Week 28, and then every 12 weeks ± 7 days.													
Tumor assessments: Chest CT, abdomen/pelvis CT/MRI; brain MRI/CT (if with baseline brain mets or symptom/sign-initiated); technetium bone scan; and CT of bone (only if clinically indicated) (Section 5.6.6)	Tumor assessments are to be performed every 9 weeks ± 7 days from the date of randomization through Week 28 (ie, the first three post-randomization tumor assessments) and then every 12 weeks ± 7 days. These assessments are to continue until meeting protocol defined criteria for discontinuing imaging irrespective of whether study treatment is given, held, or discontinued and independent of the timing of the RSVs. For subjects who discontinue study treatment before Investigator-assessed radiographic PD, tumor assessments are to continue per the protocol defined schedule until Investigator-assessed radiographic PD per RECIST 1.1. For subjects who continue to receive study treatment after Investigator-assessed radiographic PD because of Investigator-assessed clinical benefit that outweighs the potential risks, tumor assessments are to continue per the protocol defined schedule until study treatment is permanently discontinued.													
HRQOL (EQ-5D-5L and QLQ-C30; Section 5.6.8)[h]	pre-dose	HRQOL assessments will occur when scheduled imaging is performed: every 9 weeks ± 7 days through Week 28, and then every 12 weeks ± 7 days.												
Pain assessments[i] (Section 5.6.9)	pre-dose	Pain assessments will occur when scheduled imaging is performed: every 9 weeks ± 7 days through Week 28, and then every 12 weeks ± 7 days.												
PK blood samples for cabozantinib (Experimental arm)[j, k,] (Section 5.6.12)	pre-dose	pre-dose	pre-dose	pre-dose	pre-dose									
PK blood samples for atezolizumab (Experimental arm)[j, k] (Section 5.6.12)	pre-dose		pre-dose		pre-dose				pre-dose	pre-dose on RSV16	pre-dose on RSV19		X	X

	Post-Randomization											Post-Treatment	
Assessment	**RSV1 (To occur no more than 72 hours prior to 1st dose.)**	**After RSV1, subsequent RSVs are required at least every 3 weeks (ie, no more than 3 weeks apart), even if treatment is held. For atezolizumab dose delays: an RSV is required within 72h prior to each planned infusion, resetting next RSV interval**										**Unscheduled Visit[o]**	**FU-1[p]**	**FU-2[q]**
		RSV2 (±3 Days)	**RSV3 (±3 Days)**	**RSV4 (±3 Days)**	**RSV5 (±3 Days)**	**RSV6 (±3 Days)**	**RSV7 (±3 Days)**	**RSV8 (±3 Days)**	**RSV9 (±3 Days)**	**RSV10 through RSV 17 (±3 Days)**	**Each RSV after RSV17 until treatment is discontinued (±3 Days)**		**30-Day Post Treatment Follow-Up (+14 Days)**	**100-Day Extended Follow-Up (±14 Days)**
Blood samples for immunogenicity (Experimental arm)[j, k] (Section 5.6.13)	pre-dose		pre-dose		pre-dose				pre-dose	pre-dose on RSV16	pre-dose on RSV19		X	X
Optional tumor tissue[l] (Section 5.6.14)	X	An optional tumor biopsy may be collected at disease progression.												
Pharmacogenetic blood sample[m] (Section 5.6.14)	pre-dose													
Blood - plasma biomarker samples (Section 5.6.14)	pre-dose	X			X								optional	
Blood – Cell and/or plasma pharmacogenomic samples (Section 5.6.14)	pre-dose	X											optional	
Cabozantinib (Experimental Arm) dispensing/ reconciliation[r] (Sections 6.4 and 6.5)	X	X	X	X	X	X	X	X	X	X	X			
Cabozantinib (Experimental Arm) administration[n] (Sections 6.2.3.1 and 6.2.4)	X 1st dose to occur ≤ 3 days after randomization. 1st daily dose given in clinic after first dose of atezolizumab.	Subsequent daily doses self-administered by subject at home at bedtime thereafter until study treatment is discontinued.												

	Post-Randomization											Post-Treatment	
Assessment	**RSV1** **(To occur no more than 72 hours prior to 1st dose.)**	**After RSV1, subsequent RSVs are required at least every 3 weeks (ie, no more than 3 weeks apart), even if treatment is held. For atezolizumab dose delays: an RSV is required within 72h prior to each planned infusion, resetting next RSV interval**										**Unscheduled Visit[o]**	**FU-1[p]**	**FU-2[q]**
		RSV2 (±3 Days)	**RSV3 (±3 Days)**	**RSV4 (±3 Days)**	**RSV5 (±3 Days)**	**RSV6 (±3 Days)**	**RSV7 (±3 Days)**	**RSV8 (±3 Days)**	**RSV9 (±3 Days)**	**RSV10 through RSV 17 (±3 Days)**	**Each RSV after RSV17 until treatment is discontinued (±3 Days)**		**30-Day Post Treatment Follow-Up (+14 Days)**	**100-Day Extended Follow-Up (±14 Days)**
Atezolizumab (Experimental Arm) administration [n] (Section 6.2.3.1)	X 1st dose to occur ≤ 3 days after randomization. Vital signs must be assessed within 60 min prior to initiation of the infusion.	Doses of atezolizumab should be administered every 3 weeks and no more frequently than every 19 days. If atezolizumab administration is not delayed for AE management, it should be administered within 24 days of the prior atezolizumab dose. If the atezolizumab dose is delayed, subjects must have an RSV at least every 3 weeks during the delay and follow up with additional unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for resumption of study treatment. An RSV is required within 72h (and laboratory results reviewed) prior to each planned infusion, even if less than 3 weeks have elapsed since the last RSV. Vital signs must be assessed within 60 min prior to initiation of the infusion. Once atezolizumab is re-started, RSVs are to occur at least every 3 weeks (± 3 days) thereafter (ie, RSV schedule resets on date of infusion).											
Abiraterone/prednisone, or enzalutamide (Control Arm) dispensing/ reconciliation [r] (Sections 6.4 and 6.5)	X	X	X	X	X	X	X	X	X	Every 3 weeks	Every 3 weeks			
Abiraterone/prednisone, or enzalutamide (Control Arm) administration [n] (Sections 6.2.3.2 and 6.2.5)	X 1st dose to occur ≤ 3 days after randomization. 1st daily dose given in clinic.	Subsequent daily doses self-administered by subject at home thereafter until study treatment is discontinued.												

	Post-Randomization											Post-Treatment	
Assessment	**RSV1** **(To occur no more than 72 hours prior to 1st dose.)**	**After RSV1, subsequent RSVs are required at least every 3 weeks (ie, no more than 3 weeks apart), even if treatment is held. For atezolizumab dose delays: an RSV is required within 72h prior to each planned infusion, resetting next RSV interval**									**Unscheduled Visit[o]**	**FU-1[p]**	**FU-2[q]**
		RSV2 (±3 Days)	**RSV3 (±3 Days)**	**RSV4 (±3 Days)**	**RSV5 (±3 Days)**	**RSV6 (±3 Days)**	**RSV7 (±3 Days)**	**RSV8 (±3 Days)**	**RSV9 (±3 Days)**	**RSV10 through RSV 17 (±3 Days)**	**Each RSV after RSV17 until treatment is discontinued (±3 Days)**	**30-Day Post Treatment Follow-Up (+14 Days)**	**100-Day Extended Follow-Up (±14 Days)**
Non-protocol anti-cancer treatment and survival status (Section 5.6.15)													Subjects will be contacted every 8 weeks (± 7 days) after follow-up visit until death.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRF, case report form; CT, computerized tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FU-1, 30-Day Post-Treatment Follow-up Visit; FU-2, 100-Day Post-Treatment Follow-up Visit; HRQOL, health-related quality of life; IP, investigational product; LFT, liver function test; MRI, magnetic resonance imaging; NRS, numeric rating scale; PSA, prostate specific antigen; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; PD, progressive disease; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RSV, routine safety visit; SSE, symptomatic skeletal events; T4, thyroxine; TSH, thyroid-stimulating hormone; UPCR, urine protein/creatinine ratio

[a] If at any time a single ECG shows a QTcF with an absolute value > 480 ms at screening or > 500 ms at RSV1 onwards or an increase in QTcF of > 60 ms above baseline at RSV1 onwards, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used as the value assessed. If the average QTcF from the three ECGs is > 500 ms or there is an increase of > 60 ms above baseline, send ECGs to central ECG reader.

[b] See Section 5.6.5 and the Laboratory Manual for more detailed information on laboratory assessments.

[c] These assessments are not required prior to the first dose if there has been no change in subject's clinical status since screening. Serum chemistry, hematology, coagulation, and urinalysis laboratory results must be reviewed before any atezolizumab infusion administered on study. If the subject has symptoms indicative of a thyroid function disorder, thyroid function test results are to be reviewed prior to administering atezolizumab. All laboratory results (with the exception of routine urinalyses) must be provided to the local laboratory management vendor.

[d] Perform 24-hour urine protein test at the discretion of the Investigator based on increase in UPCR from routine assessments.

[e] New or increased use of analgesics from baseline will be continuously assessed by the Investigator. A new analgesic is defined as one that is taken for at least seven consecutive days after, but not prior to, randomization. Increased use of an analgesic is defined as an increased dose of an analgesic taken for at least seven consecutive days after randomization relative to the baseline dose. These assessments are to be performed regardless of whether study treatment is given, reduced, held or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects.

[f] The definition of an SSE is an instance of any one of the following: radiation therapy to bone, surgery to bone, spinal cord compression, or symptomatic fracture.

[g] Collection of hospital admissions, emergency room visits, intensive care unit admissions, length of stay and relevant procedures (eg, surgeries, radiotherapy, embolization, transfusions) from randomization through the FU-2 visit.

[h] HRQOL forms are to be administered and collected prior to any other study-related activities for scheduled visits. Questionnaires are to be completed prior to the clinic visit or if completed on the day of the visit prior to seeing the study site personnel. These assessments are to be performed regardless of whether study treatment is given, reduced, held or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects.

[i] Assessment of pain will be self-reported by each subject using an 11-point NRS measuring the worst pain in the last week. Subjects are to complete the pain assessment at the start of each clinic visit (pre-dose at RSV1). These assessments are to be performed regardless of whether study treatment is given, reduced, held or discontinued until the date of the last tumor imaging assessment or study completion. Consequently these assessments may be required in the Post-Treatment Period for some subjects.

[j] For subjects in the experimental arm, the PK samples for cabozantinib and atezolizumab are to be taken prior to atezolizumab infusion. The Investigator will ask the subject for the date and time of the most recent prior dose of cabozantinib and this information will be recorded in source documents and on the appropriate CRF page.

[k] If there is a dose delay for atezolizumab, PK and immunogenicity samples are still to be taken at the RSVs as shown. See the Laboratory Manual for more detailed information on PK and immunogenicity assessments.

[l] If no archival tumor tissue is available, an optional fresh tumor biopsy may be collected prior to first dose. Baseline tumor tissue is to be shipped within 3 weeks of first dose. An optional biopsy may be collected at disease progression. See Section 6.6.1.1.7 for guidance regarding biopsies.

[m] If collection of the required pharmacogenetic blood sample is missed on day of first dose, it can be collected subsequently.

[n] Combination of cabozantinib/atezolizumab, or abiraterone/prednisone, or enzalutamide administered until disease progression or no longer clinically benefitting.

[o] Unscheduled visits for safety evaluations are allowed at any time.

[p] A first Post-Treatment Follow-up Visit (FU-1) for safety evaluation is to occur at least 30 (+14) days after the date of the decision to permanently discontinue study treatment, defined as the later of the decision to permanently discontinue study treatment or the last dose of study treatment.

[q] A second follow up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment, defined as the later of the decision to permanently discontinue study treatment or the last dose of study treatment.

[r] Oral IP dispensing to the subject may be adjusted if RSVs are performed less than 3 weeks apart or the dose is adjusted, and the subjects has an adequate oral IP supply.

[s] If an LFT visit coincides with an RSV, duplicate LFTs do not need to be performed.

[t] Direct and indirect bilirubin assessments are not required when the total bilirubin is normal or low.

Appendix C: Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established for regulatory purposes. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase subjects will continue to receive active study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.5.1). Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests, ECG, symptom-directed physical examination and vital signs) and tumor assessments every 12 weeks (or more frequently as clinically indicated) for as long as they are in this phase.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs (Table 8-1), and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol (Section 8.2).

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

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

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2) at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the Post-Treatment Follow-up Visits. Upon initiation of the Maintenance Phase, no further follow up is required for any subject who has completed the FU-1 and FU-2 Visits.

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

See the Maintenance Phase Schedule of Assessments below. To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits may occur at a reduced frequency but must be frequent enough to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into CRFs. The safety data will continue to be collected in the Argus database, summarized in table format, and appended to the final clinical study report. Imaging data from tumor assessments during the Maintenance Phase will be collected by the sites, but not included in the final clinical study report.

Schedule of Assessments: Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment is Permanently Discontinued)	**Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2)**
Study drug accountability	Every time study drug is dispensed	✓[a]
Study treatment	Atezolizumab infusion (q3w); Cabozantinib (po qd) OR Abiraterone (po qd) + prednisone (po bid) OR Enzalutamide (po qd) Study treatment may continue until a criterion for discontinuation is met (Section 3.5.1).	-
Safety evaluation: *symptom-directed physical examination, vital signs hematology, chemistry, PT/INR, PTT, urine analysis, UPCR, thyroid function tests and ECG*	Every 12 weeks[b]	✓[a]
Reporting of SAEs, AESIs, and other reportable events (pregnancy, medication errors with sequelae)	Submit reports to Sponsor per Section 8.2	
Reporting of AEs (including AESIs): • leading to study treatment discontinuation • leading to study treatment dose modification (ie, causing study treatment to be withheld or reduced)	Submit reports to Sponsor per the same process as for reporting SAEs per Section 8.2 SAE reporting timeline requirements do not apply to non-serious events reported in these categories	
Tumor assessments: *CT of chest; CT/MRI of abdomen and pelvis; MRI (or CT) of brain (in subjects with known brain metastasis or if clinically indicated); and technetium bone scan and (if needed) CT of bone*	Every 12 weeks[b]	-

AE, adverse event; AESI, adverse event of special interest; bid, twice daily; CT, computerized tomography; ECG, electrocardiogram; FU-1, 30-Day Post-Treatment Follow-up Visit; FU-2, 100-Day Post-Treatment Follow-up Visit; MRI, magnetic resonance imaging; po, orally administered; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; q3w, every 3 weeks; qd, once daily; SAE, serious adverse event; UPCR, urine protein/creatinine ratio
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central ECG vendor.

[a] Subjects should return all unused study medication and undergo a safety evaluation per schedule of assessments.

[b] Safety and tumor assessments in the Maintenance Phase may occur more frequently as clinically indicated.

Appendix D: Performance Status Criteria

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

Appendix E: Highly Effective Methods of Contraception

In Inclusion Criterion #13 (Section 4.2), sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and until the end of relevant systemic exposure, defined as 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm).

The effect of cabozantinib on the PK of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as "effective methods of contraception," they should be used together with another method.

Contraception guidance for subjects with partner(s) of childbearing potential

Subjects with partners of childbearing potential are eligible if they agree to the following during the treatment and until the end of relevant systemic exposure, defined as 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm).

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Subjects are required to use a condom during study duration and until end of relevant systemic exposure, defined as 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm).
- Female partners of subjects in the study are to consider use of effective methods of contraception until the end of relevant systemic exposure in the male participant, defined as 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm).

Subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the

treatment and until 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm). Refrain from donating sperm these same periods.

Contraception guidance for female partners of childbearing potential

One of the highly effective methods of contraception listed below, in combination with one acceptable barrier method below, is required during study duration and until the end of relevant systemic exposure, defined as 4 months (16 weeks) after the last dose of cabozantinib in the experimental arm (cabozantinib + atezolizumab), 3 weeks after the last dose of abiraterone (control arm), or 3 months (12 weeks) after the last dose of enzalutamide (control arm). Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly effective contraceptive methods that are user dependent: These methods have a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral or injectable

Highly effective contraceptive methods that are user independent:

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system
- Intrauterine device
- Bilateral tubal occlusion

- Vasectomized partner
    - A vasectomized partner is a highly effective contraception method provided that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used
- Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
        - It is not necessary to use any other method of contraception when complete abstinence is elected.

<u>Acceptable barrier methods for use in combination with a highly effective method:</u>

- Male or female condom with or without spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide

<u>Unacceptable as a Sole Method of Contraception:</u>

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception of which inhibition of ovulation is not the primary mechanism of action

- Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods)
- Withdrawal (eg, coitus interruptus).
- Spermicide only
- Lactation amenorrhea method

Appendix F: Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could include:

- Subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low
- Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone, controlled Type 1 diabetes mellitus and on an insulin regimen, or asthma that requires intermittent use of bronchodilators
- Subjects with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis)

Caution should be used when considering atezolizumab for subjects who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anticancer agent.

The Sponsor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix G: Infusion-Related Reaction and Cytokine-Release Syndrome Guidelines

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

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 the Sponsor[f]. • Administer symptomatic treatment[c]. • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (eg, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anticytokine 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 anticytokine therapy, experimental treatments may be considered at the discretion of the Investigator and in consultation with the Sponsor.
Grade 4[a]: Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact the Sponsor[f]. • Administer symptomatic treatment[c]. • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (eg, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anticytokine therapy[e]. For patients who are refractory to anticytokine therapy, experimental treatments[g] may be considered at the discretion of the Investigator and in consultation with the Sponsor. • Hospitalize patient until complete resolution of symptoms.

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bi-level positive airway pressure; CAR, chimeric antigen receptor; CPAP, continuous positive airway pressure; CRS,cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic Case Report Form; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IRR, infusion-related reaction; MAS, macrophage activation syndrome; NCCN, National Cancer Comprehensive Network; NCI, National Cancer Institute.
Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anticytokine, 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, antipyretics, 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 anticytokine 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 subjects who are deriving benefit and have fully recovered from the event. The decision to rechallenge subjects with atezolizumab should be based on Investigator's assessment of benefit–risk and documented by the Investigator. The Sponsor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

[g] Refer to Riegler et al 2019 for information on experimental treatments for CRS.

Appendix H: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

Adapted from Eisenhauer et al 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.
- Bone lesions may only be considered measurable if there is a soft tissue component (lytic or mixed lytic-blastic) and the long axis diameter is at least 10 mm.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Leptomeningeal disease, lytic or mixed lytic-blastic bone lesions, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable. Following a time point response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are generally not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed. Following a time point response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT can be considered as measurable lesions and new lesions if the *soft tissue component* meets the definition of measurability described above.
- Purely blastic bone lesions (best identified by CT scan) do not meet the criteria for selection as target or non-target lesions or new lesions.

Lesions with prior local treatment

- Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond

the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Positron emission tomography will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study.

Bone scans may be used to assess the presence or disappearance of bone lesions.

Tumor Markers: Tumor markers may be evaluated for changes but will not be used to determine progressive disease in this study.

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is reduced, interrupted, delayed, or discontinued.

At baseline, tumors and lymph nodes are classified and documented as target or nontarget lesions per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases'). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for ‘too small to measure’ should be included in source documents.

For target lesions, measurements should be taken and recorded in metric notation.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a ‘new’ cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression cannot be based solely on bone scan findings. Bone scans are to be used to direct corroborative imaging with CT if necessary. These CT findings will be used for the determination of progression.

TIME POINT RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions).

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR / Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should normally not trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (NA)	No non-target lesions identified at screening.
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). Note: The appearance of one or more new lesions on CT or MRI scan is considered progression if these findings are unequivocally not due to a change in the imaging technique or modality. On bone scan, new lesions are not sufficient to qualify as PD. Confirmation should be obtained by performing CT of the area of concern to confirm results of bone scan.
No	No new lesions present at follow-up.
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Time Point Response			
Target Lesion TPR	**Non-target lesion TPR**	**New lesion TPR**	**Overall TPR**
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Any except PD	No	UE
PD	Any	No or Yes	PD
Any	PD	No or Yes	PD
Any	Any	Yes	PD**
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE	No	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior or subsequent time point (ie, confirmation requirement are not considered when assigning time point responses).

* Subjects with an overall response of CR or PR must have a follow-up tumor assessment performed no less than 4 weeks after the criteria for response are first met (this may be performed at the next scheduled tumor assessment). However, the presence, absence, or status at this follow up assessment is not considered when assigning a time point response at prior time points.

** If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the subject's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the subject's tumor had reached a CR status and the lesion reappeared, then the subject would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response.

Furthermore, in order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have a follow-up tumor assessment no less than 4 weeks after the initial PD criteria were met. This may be performed at the next scheduled tumor assessment. However, the presence, absence, or status at this follow up assessment is not considered when assigning a time point response at prior time points.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For subjects with an overall response of PR or CR at a given time point, a follow-up tumor assessment must be performed no less than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled tumor assessment.

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have a follow-up tumor assessment no less than 4 weeks after the initial PD criteria were met. This may be performed at the next scheduled tumor assessment.

However, the presence, absence, or status at these follow up assessments is not considered when assigning a time point response at prior time points.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

Appendix I: List of Substrates, Inducers, and Inhibitors of Selected CYP450 Isozymes

Experimental Arm (cabozantinib and atezolizumab)

Cabozantinib is a CYP3A4 substrate (Section 7.3.1).

Chronic co-administration of cabozantinib with drugs known to be strong inducers of the CYP3A4 family may decrease cabozantinib concentrations and therefore should be avoided during treatment with cabozantinib. St. John's Wort (Hypericum perforatum) is also known to be an inducer of CYP3A4 and should be avoided.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family may increase cabozantinib concentrations and should be avoided during treatment with cabozantinib. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided during treatment with cabozantinib.

Control Arm (abiraterone with prednisone, or enzalutamide)

Abiraterone

Abiraterone is a substrate of CYP3A4 (Section 7.3.3). Avoid co-administration of strong CYP3A4 inducers as they may decrease abiraterone concentrations.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8 (Section 7.3.3). Co-administration of abiraterone with CYP2D6 substrates may increase concentrations of these substrates, therefore avoid concomitant use with CYP2D6 substrates that have a narrow therapeutic index. Subjects should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone.

Enzalutamide

Avoid co-administration of enzalutamide with strong CYP2C8 inhibitors and strong CYP3A4 inducers (Section 7.3.4).

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans (Section 7.3.4). Avoid concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (eg, phenytoin) and CYP2C19 (eg, S-mephenytoin), as enzalutamide may decrease the plasma exposure of these drugs.

<table>
<tr><th>Strong Inhibitors of CYP3A4</th><th>Strong Inducers of CYP3A4</th></tr>
<tr><td>Antivirals
Boceprevir
Cobicistat
Conivaptan
Danoprevir
Dasabuvir
Elvitegravir
Indinavir
Lopinavir
Nelfinavir
Ombitasvir
Paritaprevir
Ritonavir
Saquinavir
Telaprevir
Tipranavir

Anti-Fungals
Itraconazole
Ketoconazole
Posaconazole
Voriconazole

Antibiotics
Clarithromycin
Telithromycin
Troleandomycin

Conivaptan
Diltiazem
Grapefruit juice/star fruit/Seville oranges
Idelalisib
Nefazodone</td><td>Carbamazepine
Efavirenz
Enzalutamide
Erythromycin
Mitotane
Modafinil
Nevirapine
Oxcarbazepine
Phenytoin
Rifampin
St. John’s Wort

CYP3A4 Substrates with Narrow Therapeutic Index
Alfentanil
Cyclosporine
Dihydroergotamine
Ergotamine
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus</td></tr>
<tr><td colspan="2">Strong CYP2C8 Inhibitors</td></tr>
<tr><td colspan="2">Gemfibrozil</td></tr>
<tr><td colspan="2">CYP2D6 Substrates with Narrow Therapeutic Index</td></tr>
<tr><td colspan="2">Thioridazine</td></tr>
<tr><td colspan="2">CYP2C9 Substrates with Narrow Therapeutic Index</td></tr>
<tr><td colspan="2">Phenytoin</td></tr>
<tr><td colspan="2">CYP2C19 Substrates with Narrow Therapeutic Index</td></tr>
<tr><td colspan="2">S-mephenytoin</td></tr>
</table>

This table is not all-inclusive. Please refer to the FDA website for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Appendix J: Collection, Follow-Up, and Documentation Requirements for AEs, AESIs, and SAEs

All adverse events (AEs) that are not serious and not AESIs (AEs of special interest; Table 8-1) that start or worsen after the first dose of study treatment through the 30-day post-treatment follow-up (FU-1) visit are to be entered into the electronic CRF data capture system (EDC). Such events continuing at the FU-1 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes. These events do not require a Drug Safety SAE report to be completed.

Additional requirements apply to the following events:

- All serious adverse events (SAEs) that are judged by the Investigator to be not related to study treatment that start or worsen after the subject's initial informed consent through the 100-day post-treatment follow-up (FU-2) visit are to have a Drug Safety SAE report completed. Such events continuing at the FU-2 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes.
- All AEs leading to study treatment discontinuation that are judged by the Investigator to be related to study treatment that are continuing at the FU-2 visit are to be followed by the Investigator until resolution, defined as: fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required. If serious, the requirements for related SAEs apply.
- All AESIs (regardless of seriousness) that start or worsen after the subject's initial informed consent through the FU-2 visit are to have a Drug Safety SAE report completed and be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution, with evidence of resolution provided on updates to the Drug Safety SAE report. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.
- All SAEs that are judged by the Investigator to be related to study treatment that start or worsen at any time after the subject's initial informed consent are to have a Drug Safety SAE report completed. Such events that occur prior to the FU-2 visit are to be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution, with evidence of resolution provided on updates to the Drug Safety SAE report. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.

Summaries of the event surveillance (Table J-1) and follow-up requirements (Table J-2) are shown in the following page:

Table J-1: Requirements for Documenting the Incidence of AEs, SAEs and AESIs

Event type	Event surveillance period (inclusive):			
	EDC CRF[a]		Drug Safety SAE Report	
	Period start	Period stop	Period start	Period stop
AE: nonserious, non-AESI	first dose	FU-1	NA	NA
SAE: not related	IC	FU-2	IC	FU-2
Related AE leading to study treatment discontinuation	first dose	EOT date	NA (if nonserious)	NA (if nonserious)
AESI: nonserious (AESIs: irAEs, potential DILI, Other; Table 8-1)	IC	FU-2	IC	FU-2
Related SAE	IC	FU-2	IC	ever
All Deaths	IC	End of Trial	IC	FU2

AE, adverse event; AESI, adverse event of special interest (Table 8-1); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 (+14) days after EOT date; FU-2, follow-up visit 100 (±14) days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

Table J-2: Requirements for Following up on Events Documented and Reported as Defined in Table J-1

Event type	Event follow-up requirements				
	If ongoing at…	…follow until…	…and document following on:		
			Source documents	EDC CRF[a]	Drug Safety SAE Report
AE: nonserious, non-AESI	FU-1	NA	status at FU-1	status at FU-1	NA
SAE: not related, non-AESI	FU-2	NA	status at FU-2	status at FU-2	status at FU-2
Related AE leading to study treatment discontinuation	FU-2	Resolution[b]	evidence of resolution	status at FU-2	NA (if nonserious)
AESI: regardless of seriousness (AESIs: irAEs, potential DILI, Other; Table 8-1)	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution
Related SAE	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution

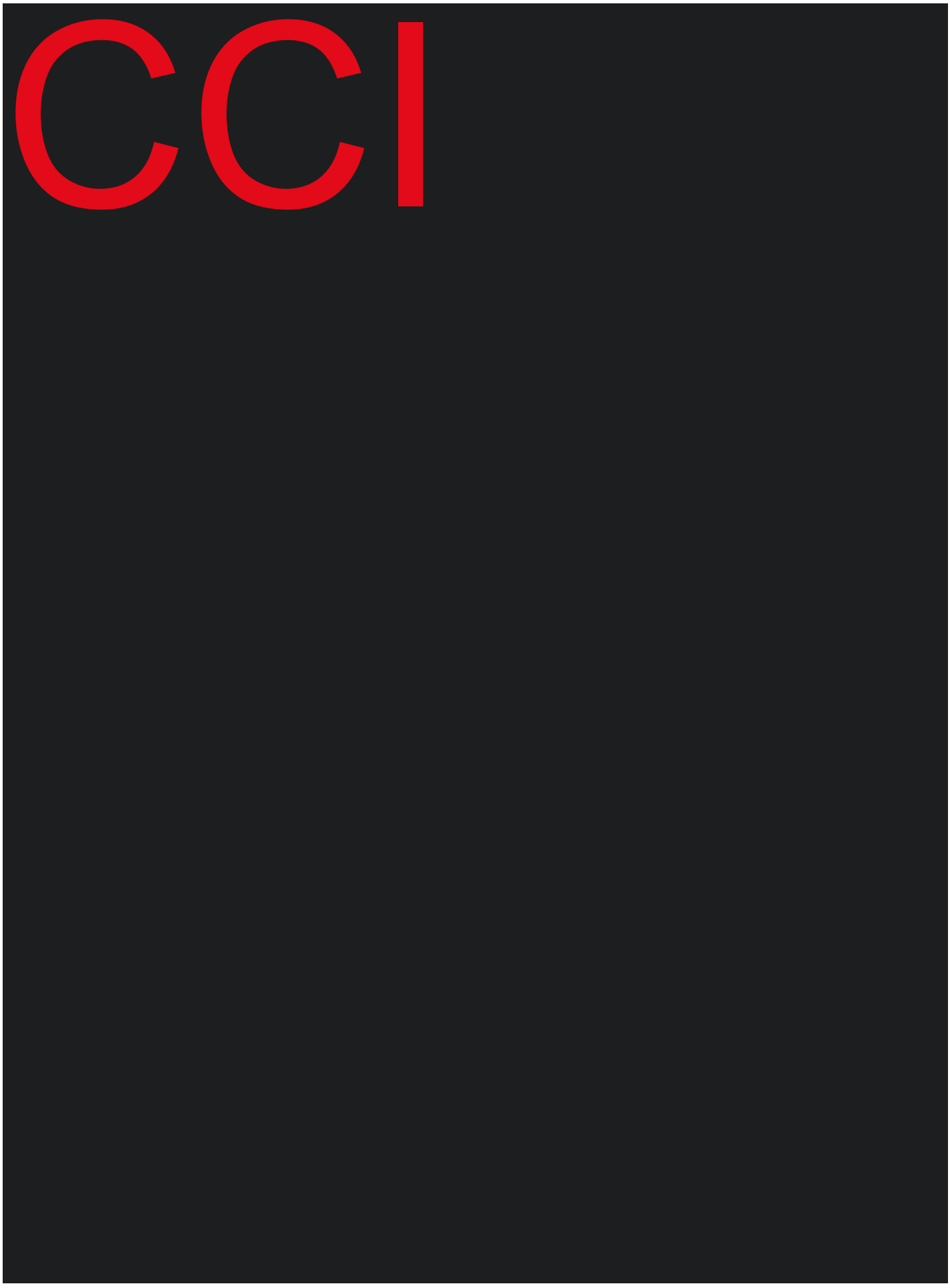
AE, adverse event; AESI, adverse event of special interest (Table 8-1); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 (+14) days after EOT date; FU-2, follow-up visit 100 (±14) days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

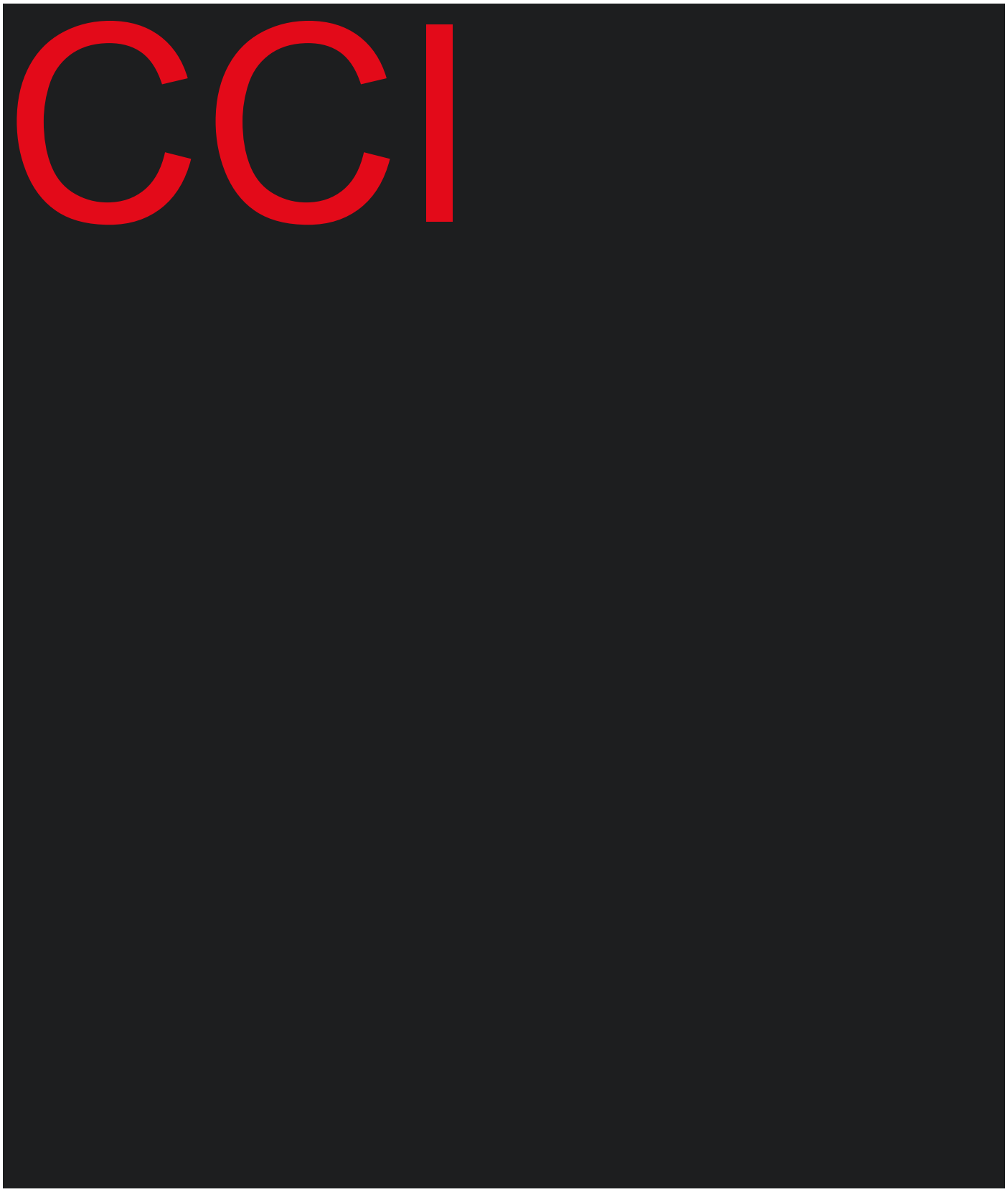
[b] Defined as: AE is fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator

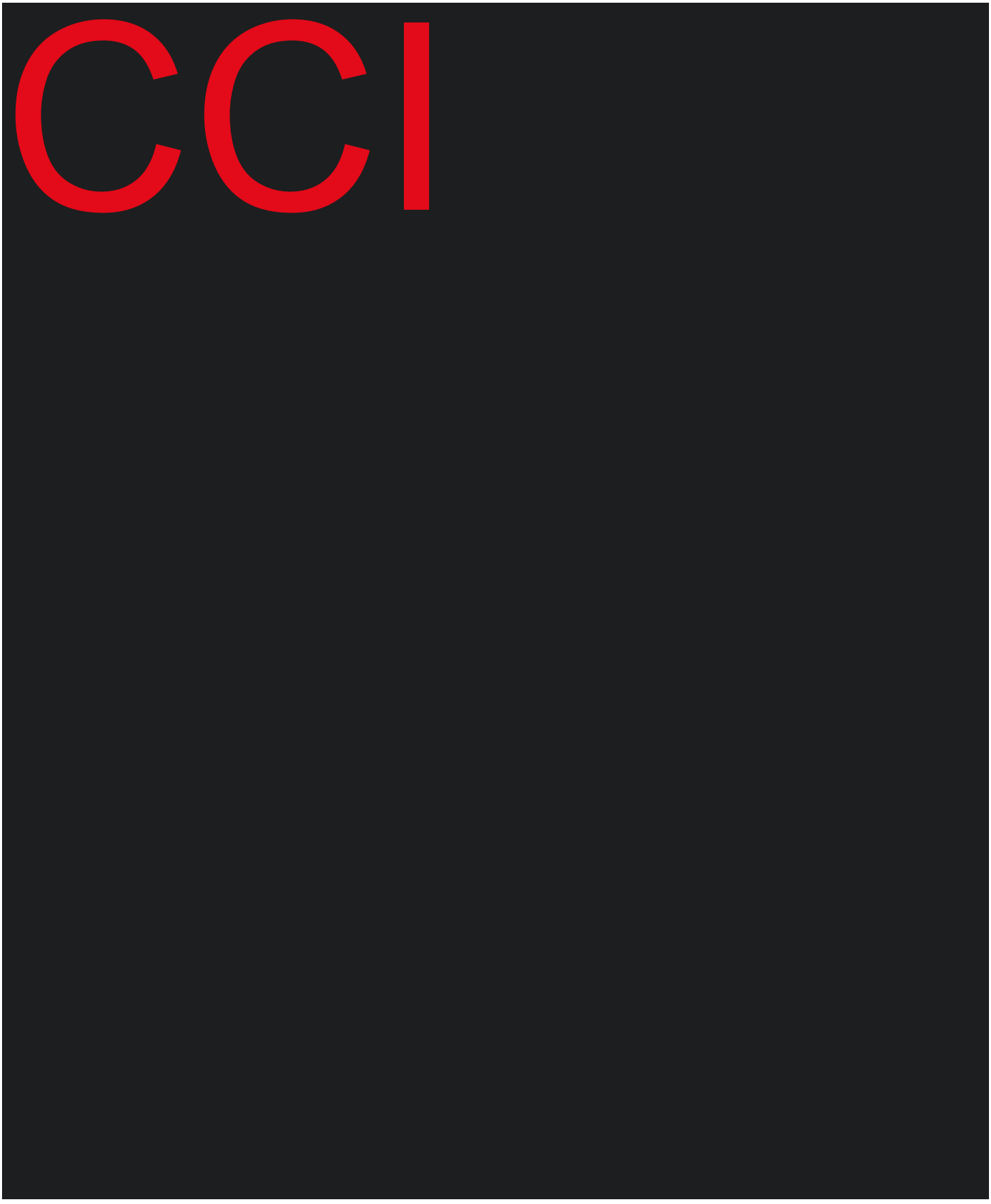
Appendix K: EuroQoL Questionnaire EQ-5D-5L, USA (English) Sample Version

Under each heading, please the ONE box that best describes your health TODAY.


CCI

Appendix L: EORTC QLQ-C30 Questionnaire, English Sample Version 3




CCI

Appendix M: 11-point Numeric Rating Scale (NRS) for Pain Assessments

Appendix N: COVID-19 Instructions

This appendix describes contingencies and accommodations for sites and subjects impacted by the COVID-19 pandemic. In response to the evolving circumstances of the pandemic, the Sponsor will provide ongoing guidance to Investigators on study conduct to ensure subject safety and maintain the scientific integrity of the study. Investigators must also maintain awareness of and respond to instructions and guidelines from their local regulatory authorities during the pandemic. These will be temporary measures and are applicable only during the pandemic, and as necessary to abide by local public health requirements. These measures will be repealed back to the measures described in the full study protocol, including Appendix A, Appendix B, and Appendix C, as soon as the situation (governmental rules, benefit/risk assessment for the trial) allows.

Under the exceptional circumstances of the COVID-19 pandemic where randomized subjects are not able or willing to physically access the site clinic, the following accommodations may be permitted if allowed by local and other applicable regulations (Note: special accommodations are not permitted for screening assessments):

- Safety assessments should still be performed unless the Investigator and Sponsor agree that specific assessments may be missed as long as this occurs in accordance with all applicable local regulations. However, at a minimum, the Investigator or designee must regularly contact the subject (eg, by phone) to ascertain the subject's condition and occurrence of any symptom-based AEs per the relevant protocol-defined visit schedule. If available, results of any remote assessments performed by a non-study local oncologist or primary care physician must be sent to the Investigator for review and documentation. If components of the safety assessment cannot be collected or the timing of safety assessments needs to be adjusted, it may be possible to continue with study treatment but this will have to be discussed on a case-by-case basis with the Medical Monitor. Any remote laboratory assessments must be performed by laboratories accredited by the local jurisdiction.

- Tumor assessments may be performed at another radiology facility rather than at the study site (this option is not available in Germany). Such facilities should perform tumor assessments in accordance with the protocol, but alternative image acquisition protocols (eg, single post-contrast vs triple phase) may be accepted if the preferred modality is not available. The treatment modality (eg, CT scan or MRI) should be the same as that utilized since the start of study entry in order to avoid discrepancies in imaging interpretation. Imaging should be performed within or as close to the study visit window for scheduled

imaging time points as possible. The study site must collect tumor images generated off site in a timely fashion for review and documentation by the Investigator and submission to the BIRC.

- Alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations. Confirmation of drug receipt will be obtained by sites.

- Intravenous study treatment should generally only be administered at the study site, but circumstances may arise where the subject may receive infusions in another location under the supervision of the Investigator, with the approval of the Sponsor, and in accordance with all applicable regulations.

If logistical challenges in providing study treatment or performing study-related assessments result in temporary interruption of all study treatment for greater than 12 weeks, subjects are required to permanently discontinue study treatment unless permitted to continue by the Sponsor.

If it becomes necessary to employ any of the accommodations described in this appendix of COVID-19 Instructions, Investigators are to document each incident in source records as COVID-related. To comply with emerging regulatory guidance that such accommodations be reported and their impact on the study assessed, these will be collected by the Sponsor (or designee) as protocol-deviations. However, no corrective action will generally be expected if this appendix is followed.

Subjects are to be informed of changes to standard procedures resulting from effects of the COVID-19 pandemic, and if necessary, subject consent is to be acquired. If additional consent is necessary during the course of the study but cannot be immediately obtained from the subject in writing, the Investigator is to describe to the subject the additional information requiring consent, obtain verbal consent from the subject, document such consent in the subject file, and follow up with written consent the next time a subject returns to the site. This does not apply to initial consent to enter the study; in this case, written consent is still required.

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

Any cases of confirmed or suspected COVID-19 infections should follow the general AE reporting requirements defined in the protocol. For any confirmed or suspected COVID-19 cases,

the Investigator is responsible for assessing if the event should be reported as a SAE using their clinical judgment. The Investigator should further consider whether the diagnosis meets the criteria of being a significant medical event.

When recording data missing, impacted, or related to COVID-19 in the electronic CRFs, the conventions below are to be employed. Also refer to updated CRF Completion Guidelines and site communication memos for additional instructions for how to document data missing or impacted by COVID-19.

Case Report Form	**Instructions**
Adverse Event CRF	• Record COVID-19 diagnoses as "COVID-19" • Record suspected cases as "suspected COVID-19" • If death is the outcome of such an event, the CTCAE grade should be assigned as '5'. See the CRF instructions for how to enter fatal events that started at a lower grade
End of Study Treatment CRFs	• Investigators are to use their best judgment to identify the primary reason for study treatment discontinuation. • If study treatment ended primarily due to a logistical issue associated with the COVID-19 pandemic and was unrelated to cancer progression or any AE: o Indicate "Other" as the reason for treatment discontinuation and describe the reason in the Specify field, including the term "COVID-19". For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions " • If study treatment ended primarily due to an AE caused by COVID-19 or suspected COVID-19: o Indicate "AE/SAE unrelated to progression of disease under study" o Record the AE on the Adverse Event CRF as described above with Action Taken = "Treatment Discontinued"
End of Radiographic Follow-Up CRF	• If radiographic assessments ended primarily due to a logistical issue or AE caused by COVID-19 or suspected COVID-19: o Indicate "Other" as the reason for discontinuation and describe the reason in the Specify field, including the term "COVID-19." For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions " or "Subject discontinued due to hospitalization for suspected COVID-19." In the latter example, also record the AE on the Adverse Event CRF as "suspected COVID-19"
Study Treatment CRFs	• If study treatment was held or delayed solely due to a logistical issue associated with the COVID-19 pandemic: o For oral study treatment CRFs: Indicate "Other" as the reason the dosing interval ended and describe the reason in the Specify field, including the term "COVID-19".

	○ For IV dosing CRFs: Enter “Yes” for “Dose delayed from prior infusion” and “Reason for dose delay” should be entered as “Other” and describe the reason in the Specify field, including the term “COVID-19” (if/when ‘Specify’ field is available) For example – Other, Specify: “Subject unable to travel due to COVID-19 restrictions”